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Health and Environmental Effects Profile for Brominated Dibenzo-p-dioxins and Dibenzofurans

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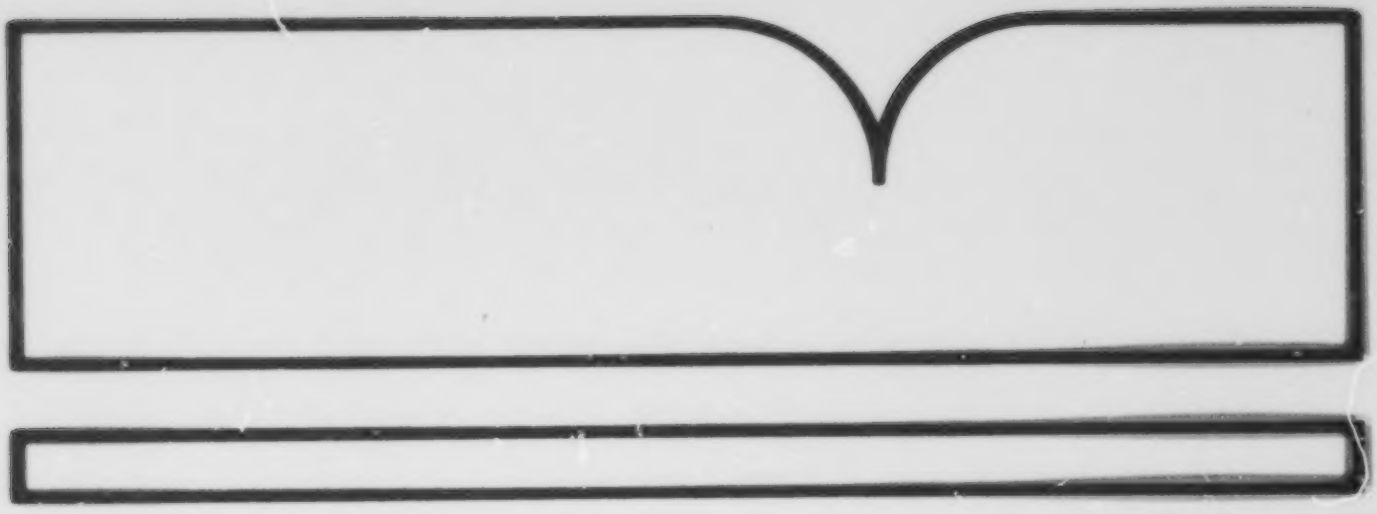

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16. ABSTRACT

The Health and Environmental Effects Profile for Brominated Dibenzo-p-dioxins and Dibenzofurans was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine a Reference Dose (RfD) or a carcinogenic potency factor for brominated dibenzo-p-dioxins and dibenzofurans.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR BROMINATED DIBENZO-p-DIOXINS AND DIBENZOFURANS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

Brominated dibenzo-p-dioxins and dibenzofurans can exist in 75 and 135 possible isomeric forms, respectively; of these, only a few compounds have been prepared and characterized. Parameters, including water solubility, K_{ow}, vapor pressure, K_{oc}, light absorption characteristics and BCFs, necessary for the prediction of environmental fate and transport of these compounds have been estimated for a few dibrominated and tetrabrominated isomers. Physical properties for structurally-related polybrominated compounds were studied to establish a general trend of increase in K_{ow} and K_{oc} and a decrease in vapor pressure and aqueous solubility as the number of halogen substitutions increased.

A likely source of PBDDs and PBDFs in the environment is pyrolysis of PBBs (Pomerantz et al., 1978; Buser et al., 1978), 2,4,6-tribromophenol, pentabromophenol, tetrabromobisphenol A (Thoma et al., 1986) and polybrominated diphenylether (Buser, 1986). Since elevated temperatures are used during the manufacture of chemicals and the incineration of waste materials, the PBDDs and PBDFs are expected to be present in the precursor materials (for example, 2,4,6-tribromophenol) and in emissions from incineration processes involving the precursor materials. Since the total amount of bromine consumption is ~50 times lower than chlorine consumption (CMR, 1982, 1983), the levels of PBDDs and PBDFs are expected to be 1 order of magnitude lower than the corresponding chlorinated products.

No experimental data on the fate and transport of these compounds in the environment are available. Based on the limited data available for the polychlorinated compounds and fate modeling from the physical properties of

the polybrominated compounds, some speculations about their fate and transport in the environment have been made. Generally, the persistence of polybrominated compounds in different environmental media is increased with an increase in bromine substitution. In air, these compounds may be removed by slow photodegradation, and dry and wet deposition, but are expected to be persistent in the atmosphere. In water, the PBDDs and PBDFs may undergo slow photolysis, biodegradation, volatilization and a strong sorption onto suspended particulates and sediments, and are expected to persist in water as well. These compounds will undergo substantial bioaccumulation in aquatic organisms. In soils, they are also expected to be persistent, strongly sorbing to soil and remaining essentially immobile there. Under normal conditions, none of these compounds will leach to groundwater. Transport may occur from soil to surface water by runoff water and from soil to the atmosphere through airborne dust particles.

Polybrominated dibenzo-p-dioxins and dibenzofurans have never been detected in air, water, soil or any environmental media. The complete absence of monitoring data may indicate the lack of effort made to identify and quantify these compounds rather than their absence in any environmental media.

Qualitatively, the chlorinated and brominated aromatic hydrocarbons appear to have similar pharmacokinetic behavior. For those halogenated homologues for which data are available, it appears that gastrointestinal absorption occurs rapidly and to a similar extent regardless of whether the halogen is bromine or chlorine (Albro and Fishbein, 1972; Matthews and Anderson, 1975a; Morales et al., 1979; Matthews et al., 1977; Tuey and Matthews, 1980).

Following absorption, the halogenated hydrocarbons form a loose association with the lipoproteins of the blood (Matthews et al., 1984; Becker and Gamble, 1982; Maliwal and Guthrie, 1982; Birnbaum, 1985), rapidly distribute from the bloodstream to highly vascular tissues and muscle (Matthews and Anderson, 1975a,b; Matthews et al., 1974) and then redistribute to fat or tissue as terminal depots of storage (Birnbaum, 1985). The placenta appears to be a partial barrier to the transfer of these compounds to the fetuses of animals (Lucier et al., 1977; Vodicnik, 1986; Vodicnik and Lech, 1980; Bleavins et al., 1981) and humans (Eyster et al., 1983).

Metabolism appears to be a prerequisite for the efficient excretion of most of the halogenated aromatic hydrocarbons (Birnbaum, 1985). The primary step is oxidation, apparently through an arene oxide intermediate (Kohli et al., 1976; Ogino, 1984a,b; Ruzo et al., 1976a,b; Kato et al., 1980; Matthews and Anderson, 1975a). There appear to be few major differences in metabolism between homologous chlorinated and brominated compounds, although the relative proportions of oxidation products resulting from the isomerizations of the arene oxide intermediates may differ (Ruzo et al., 1976a; Ogino, 1984a). Generally, for the halogenated benzenes, naphthalenes and biphenyls, the rate of metabolism decreases with increasing halogenation (Ruzo et al., 1976a; Ogino, 1984a; Moore et al., 1980; Safe, 1980) although for the biphenyls metabolism is enhanced by the presence of adjacent unsubstituted carbon atoms and, in particular, by unsubstituted para positions on at least one ring (Safe, 1980; Moore et al., 1980).

The rates of excretion of the halogenated aromatic hydrocarbons depend primarily on their rates of metabolism (Birnbaum, 1985). Comparative data with chlorinated and brominated monohalobenzene (U.S. EPA, 1977) and homologous hexahalogenated PCB and PBB (Kato et al., 1980; Birnbaum, 1983;

Matthews et al., 1977; Tuey and Matthews, 1980) suggest that the routes and rates of elimination of the chlorinated compounds are similar to the brominated compounds. Lactation is an important route of excretion for those PCBs and PBBs that resist metabolism and tend to accumulate in body fat.

The only study that compared toxicities of brominated and chlorinated dibenzofurans directly was that of Moore et al. (1979), who administered single oral doses of 1-49 nmol/kg 2,3,7,8-TCDF or 2,3,7,8-TBDF to guinea pigs. Mortality and decreased body weight gain occurred at about the same dosages for both compounds. Animals that died exhibited a similar pattern of histopathological lesions, including epithelial hyperplasia in the renal pelvis, ureter and urinary bladder, and loss of lymphoid cells in the thymic cortex.

Most of the other information presented in this chapter pertained to PCBs and PBBs, which were found to cause similar patterns of toxic effects. The structure-toxicity relationships for pure isomers also appeared to be similar for both PCBs and PBBs.

The available comparative information concerning carcinogenicity of brominated and chlorinated aromatic compounds pertains to PBBs and PCBs. Because most of this information involved commercial mixtures of these compounds, it was not useful for comparisons. In vitro assays with pure isomers indicated qualitative similarities in the tumor-promoting activities of PBB and PCB analogs (Sleight, 1985; Tsushimoto et al., 1982b, 1983).

Most of the information concerning reproductive effects of brominated and chlorinated aromatic compounds applies to PCBs and PBBs and is generally useful only for qualitative comparisons. Analogous hexachloro- and hexabromobiphenyl compounds (2,2',4,4',5,5') did not cause any fetotoxic or teratogenic effects in mice receiving oral doses of 0.3-32.0 mg/kg/day on

days 10-16 of gestation (Lucier et al., 1977). The only other study in which PCBs and PBBs were compared directly was that of Aulerich and Ringer (1977, 1979), who fed diets containing commercial PCB and PBB mixtures to mink. The PCB mixture caused more severe reproductive effects, but this result is of questionable significance because the mixtures differed in isomeric composition, degree of halogenation and level of impurities, in addition to the differences in chlorine and bromine substitution.

Quantitative structure-activity relationships have been extensively characterized for chlorinated dioxins, dibenzofurans and biphenyls (Bandiera et al., 1983, 1984; Leece et al., 1985; McKinney et al., 1984, 1985a,b; Poland et al., 1983; Safe, 1986; Safe et al., 1985a, b). Less information is available on the relative potencies of brominated aromatics than the chlorinated aromatics. In early studies on receptor binding and enzyme induction (Kende et al., 1974; Poland et al., 1976), the general relationship of biological activity with respect to differing halogen substituents appeared to follow the order: Br>Cl>F for a series of halogenated dioxins. Some exceptions to this pattern have been noted (Bradlaw and Casterline, 1979; Bradlaw et al., 1980), but differences in biological activity are generally within a factor of 3 for studies indicating that chlorinated dioxins are more potent than the corresponding brominated dioxins. Quantitative structure-activity relationships for a series of 7-substituted 2,3-dichlorodibenzo-p-dioxins indicate that receptor binding is highly correlated with lipophilicity and that AHH and EROD induction are correlated with lipophilicity as well as a steric parameter. Both the 7-chloro- and 7-bromo-substituted dioxins bound with about equal affinity to the Ah receptor, but the bromo-substituted compound was a more potent inducer of AHH and EROD by a factor of ~6 (Denomme et al., 1985).

Similar relationships have been noted for two series of dibenzofurans: 8-substituted 2,3-dichlorodibenzofurans and 8-substituted 2,3,4-trichlorodibenzofurans (Denomme et al., 1986). For both series, receptor binding was correlated with lipophilicity. For the former series, both AHH and EROD are correlated with lipophilicity and a steric parameter. For the latter series, AHH induction was related to lipophilicity, a steric parameter, as well as a parameter for electronegativity. The most substantial difference between the 8-chloro- and 8-bromo-substituted compound in both series is in EROD induction, for which the 8-chloro-substituted 2,3,4-trichlorodibenzofuran was more potent than the corresponding 8-bromosubstituted isomer by a factor of 3.

Structure-activity relationships for the receptor binding of halogenated biphenyls are substantially more complex than those for the chlorinated dioxin and dibenzofuran series summarized above. For a series of 4'-substituted 2,3,4,5-tetrachlorobiphenyls, parameters for lipophilicity, electronegativity and hydrogen bonding were required to account for the effects of structure on receptor binding (Bandiera et al., 1982). Most studies on biphenyls which allow for a direct quantitative comparison of comparative potency of chlorinated and brominated compounds clearly indicated that brominated compounds are more potent (Bandiera et al., 1982; Ecobichon et al., 1977; Andrus et al., 1983). In one study (Parkinson et al., 1983) quantitative comparisons were more difficult and the results were equivocal.

Structure-activity relationships for other brominated and chlorinated aromatics have not been well-defined. The limited available data suggest that 2,3,7,8-tetrabromonaphthalene and 2,3,7,8-tetrabromobiphenylene are more potent AHH inducers than the corresponding chlorinated isomers (Poland and Knutson, 1982; Poland and Glover, 1977).

The brominated dioxins and dibenzofurans have not been tested for carcinogenicity, mutagenicity, teratogenicity and chronic or subchronic toxicity. Therefore, risk assessments following generally accepted guidelines such as U.S. EPA (1980d) cannot be conducted for these compounds. Nonetheless, the limited available information suggests that these brominated aromatic compounds have toxicological properties and potencies comparable with the corresponding chlorinated compounds. This is consistent with the conclusion reached by U.S. EPA (1985c) in the Agency's proposed rule for requiring that certain commercial products be analyzed for selected brominated dioxins and dibenzofurans.

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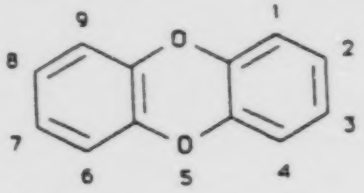
LIST OF ABBREVIATIONS

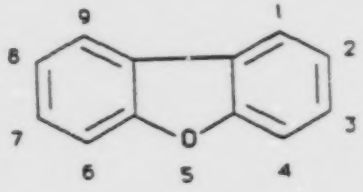
AHH	Aryl hydrocarbon hydroxylase
ALA	Aminolevulinic acid
BCF	Bioconcentration factor
bw	Body weight
CDD	Chlorinated dibenzodioxin
EC_{50}	Concentration effective to 50% of recipients
ED_{50}	Dose effective to 50% of recipients
EROD	Ethoxyresorufin O-deethylase
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
MFO	Mixed function oxidase
PBB	Polybrominated biphenyl
PBDD	Polybrominated dibenzo-p-dioxin
PBDF	Polybrominated dibenzofuran
PCDD	Polychlorinated dibenzodioxins
PCDF	Polychlorinated dibenzofuran
PCP	Pentachlorophenol
PeCDD	Pentachlorodibenzo-p-dioxin
ppb	Parts per billion
ppm	Parts per million
TCDD	Tetrachlorodibenzo-p-dioxin
UV	Ultraviolet
w/w	Wet weight

1. INTRODUCTION

Brominated dibenzo-p-dioxins and dibenzofurans are two closely related classes of compounds that have substituted bromines at different ring positions of the dibenzo-p-dioxin and dibenzofuran nucleus, respectively. The accepted system of numbering substituents to the nucleus is as follows:



Dibenzo-p-dioxin



Dibenzofuran

Polybrominated dibenzo-p-dioxins and dibenzofurans are compounds with 2-8 bromines substituted on the dibenzo-p-dioxin or dibenzofuran ring. Brominated dibenzo-p-dioxins and dibenzofurans can exist in 75 and 135 possible isomers, respectively (Table 1-1); of these, only a few compounds have been prepared and characterized.

1.1. PHYSICAL AND CHEMICAL PROPERTIES

The physical properties and BCFs of brominated dibenzo-p-dioxins and dibenzofurans are shown in Tables 1-2 and 1-3. The vapor pressure values reported for dibenzo-p-dioxin and its chlorinated isomers (see Table 1-2) were obtained from a plot of log P (P = vapor pressure) vs. 1/T (T = temperature) given by Rordorf (1985), since the numerical vapor pressure values, with the exception of one isomer (2,3,7,8-), were not reported. The vapor pressure values for tetrachloro- and octachlorodibenzo-p-dioxin have been obtained by extrapolation of data from higher temperatures to 25°C. Rordorf (1985) concluded that the vapor pressures of chlorinated dibenzo-p-dioxins were linearly proportional to the number of chlorine substitutions.

TABLE 1-1

Total Number of Possible Isomers for
Brominated Dibenzo-p-dioxin and Dibenzofuran

Number of Bromine Substitution	Compound Prefix	Number of Isomers	
		Dibenzo-p-dioxin	Dibenzofuran
1	mono-	2	4
2	di-	10	16
3	tri-	14	28
4	tetra-	22	38
5	penta-	14	28
6	hexa-	10	16
7	hepta-	2	4
8	octa-	1	1
Total number of congeners		75	135

TABLE 1-2

Physical Properties and BCFs of Chlorinated and Brominated Dibenzo-p-dioxins in Aquatic Organisms

Compound (Molecular weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure (mm Hg)	K_{oc}	UV Absorption Spectra	BCF
Dibenzo-p-dioxin $C_{12}H_8O_2$ (184.20)	120-122[a]	NA	4.17-4.57[b,c,d]	0.76×10^{-4}[e] at 25°C	NA	248[f]	NA
Chlorodibenzo-p-dioxin $C_{12}H_7ClO_2$ (218.64)	87-90[a] (2-)[g] 104.5-105.5[f] (1-)	NA	4.75-5.23[b,c,d] (1-) 5.29-5.69[b,c] (2-)	0.2×10^{-4}[e] at 25°C (1- & 2-)	NA	248[f] (1-) 294[f] (2-)	NA
Bromodibenzo-p-dioxin $C_{12}H_7Br_2O_2$ (263.09)	104-106[a] (1-) 93-945[a] (2-)	NA	NA	NA	NA	NA	NA
Dichlorodibenzo-p-dioxin $C_{12}H_6Cl_2O_2$ (253.09)	113.5- 114.5[j,k] (1,3-) 159-164[j,k] (2,3-) 201-203[a] (2,7-)	[6 µg/ℓ[h]][l] (2,7-)	6.17-6.71[b,c,d] (2,7-) [4.71[h]]	0.3×10^{-5}[e] at 25°C (2,3- & 2,8-)	[4.60]	299[j] (2,3-) 296[j] (1,3-)	[1995[h]]
Dibromodibenzo-p-dioxin $C_{12}H_6Br_2O_2$ (341.99)	157.5-158[j,k] (2,3-) 174-176[a] (2,7-) 145-151[a] (2,8-)	[9 µg/ℓ[h]] (2,3-) [11 µg/ℓ[h]] (2,8-)	NA	NA	[6.37[h]] (2,3- & 2,8-)	308[j] (2,3-)	[87,096[h]] (2,3- & 2,8-)
Tetrachlorodibenzo-p-dioxin $C_{12}H_4Cl_4O_2$ (321.98)	188-190[j,k] (1,2,3,4-) 194-195[j] (1,3,7,8-) 305-307[j,k] (2,3,7,8-)	12.5-19.3 ng/ℓ at 22°C[m] (2,3,7,8-) 200 ng/ℓ[n] (2,3,7,8-)	8.07-8.97[b,c,d] (1,2,3,4-) 7.72-8.81[b,c,d] (1,2,3,7-) 8.12-9.43[b,c,d] (1,3,6,8-) [6.15[l]] [6.15-7.28[o]] (2,3,7,8-)	3.4×10^{-6} at 25°C (1,2,3,4- & 2,3,7,8-)[e] 4.03×10^{-6}[b] at 20°C (1,3,6,8-) $1-1.7 \times 10^{-6}$[o]	[5.67[l]] (1,2,3,4- & 2,3,7,8-) [6.0-6.52[o]] (2,3,7,8-)	306[j] (2,3,7,8-) 305[j] (1,3,6,8-)	5400-35,500[l] (2,3,7,8-)
Tetrabromodibenzo-p-dioxin $C_{12}H_4Br_4O_2$ (499.78)	334-336[a,j,k] (2,3,7,8-)	[10 ng/ℓ[h]] (2,3,7,8-)	[8.53[h]]	NA	7.99[h] (2,3,7,8-)	308[j] (2,3,7,8-)	[1,778,280] (2,3,7,8-)
Pentachlorodibenzo-p-dioxin $C_{12}H_3Cl_5O_2$ (356.42)	240-241[p] (1,2,3,7,8-) 195-196[f] (1,2,3,4,7-)	[40 ng/ℓ[o]] at 25°C	8.64-10.05[b,c,d] (1,2,3,6,7-)	NA	[6.70[o]]	300[p] (1,2,3,7,8)	NA

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TABLE 1-2 (cont.)

Compound (Molecular weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure (mm Hg)	K_{oc}	UV Absorption Spectra	BCF
Pentabromodibenzo-p-dioxin $C_{12}H_3Br_5O_2$ (578.68)	NA	NA	NA	NA	NA	NA	NA
Hexachlorodibenzo-p-dioxin $C_{12}H_2Cl_6O_2$ (390.87)	285-286[q] (1,2,3,6,7,8-) 243-244[q] (1,2,3,7,8,9-)	[8 ng/ℓ[o]] at 25°C	9.19-10.87[b,c,d] (1,2,3,4,7,8-)	NA	[7.48[o]]	316[q] (1,2,3,6,7,8-) 317[q] (1,2,3,7,8,9-)	NA
Hexabromodibenzo-p-dioxin $C_{12}H_2Br_6O_2$ (657.57)	NA	NA	NA	NA	NA	NA	NA
Octachlorodibenzo-p-dioxin $C_{12}Cl_8O_2$ (459.76)	330[f]	0.4 ng/ℓ[b] at 20°C 2.14 ng/ℓ	10.07-13.48[b,c,d,r]	0.3×10^{-12}[e] at 25°C 0.13×10^{-6}[b] at 20°C	NA	318[f]	NA
Octabromodibenzo-p-dioxin $C_{12}Br_8O_2$ (815.36)	NA	NA	NA	NA	NA	NA	NA

[a]Gilman and Dietrich, 1957
[b]Webster et al.,1985
[c]Sarna et al., 1984
[d]Webster et al., 1984
[e]Rordorf, 1985
[f]IARC, 1977
[g]The numbers in parentheses represent the specific isomeric form of the compound. In some cases, the methods used to estimate the values did not differentiate between isomers.
[h]U.S. EPA, 1985a
[i]Numbers within brackets are estimated.
[j]Kende and Wade, 1973
[k]Kende et al., 1974
[l]Kenaga, 1980
[m]Marple et al., 1986
[n]Crummett and Stehl, 1973
[o]U.S. EPA, 1985b
[p]Gray et al., 1976
[q]Gray et al., 1975
[r]Webster et al., 1983
NA - Not available

TABLE 1-3

Physical Properties of Brominated and Chlorinated Dibenzofurans

Compound (Molecular Weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure[a] (mm Hg)	K_{oc}	UV Absorption Spectra
Dibenzofuran $C_{12}H_8O$ (168.21)	82.8-83.0[b]	3.11[c] at 25°C	2.95-4.17[d,e]	[1.75×10^{-2}[f]] at 25°C	941[f]	300[f]
Chlorodibenzofuran $C_{12}H_7ClO$ (202.66)	106[g] (2-)[h] 101[g] (3-)	NA	NA	NA	NA	~300[f] (2-) ~300[f] (3-)
Bromodibenzofuran $C_{12}H_7BrO$ (247.10)	67 (1-)[g] 110 (2-)[g] 120 (3-) 67-72 (4-)[g]	NA	NA	NA	NA	310[f] (2-) 300[f] (3-)
Dichlorodibenzofuran $C_{12}H_6Cl_2O$ (237.09)	185 (2,8-)[i] 186-188 (3,7-)[j]	NA	5.65-6.15[d,e]	[7.3×10^{-4}[k]] (2,4-) [7.0×10^{-4}[k]] (3,7-) [6.8×10^{-4}[k]] (2,8-)	NA (2,4-)	290[l] (2,8-)
Dibromodibenzofuran $C_{12}H_6Br_2O$ (325.99)	191.5-200[f,g] (2,8-)	NA	NA	NA	NA	NA
Tetrachlorodibenzofuran $C_{12}H_4Cl_4O$ (305.98)	169-170[g] (1,2,3,4-) 202-203[m] (2,3,6,8-) 198-200[m] (2,4,6,8-)	NA	NA	[2×10^{-4}[k]] (2,3,7,8-) $1.8-2.5 \times 10^{-4}$[k] (other isomers)	NA	314[m] (2,3,6,8-) 323[k] (2,3,7,8-) 316[k] (2,4,6,8-)
Tetrabromodibenzofuran $C_{12}H_4Br_4O$ (483.78)	NA	NA	NA	NA	NA	NA
Pentachlorodibenzofuran $C_{12}H_3Cl_5O$ (340.42)	225.5-226.5[j] (1,2,4,7,8-) 234-235[m] (1,2,4,7,8-)	NA	NA	[1.1×10^{-4}[k]] (1,2,3,6,7- &) 2,3,4,7,8) [1.3×10^{-4}[k]] 1,3,4,7,8- &) 1,2,4,7,8-)	NA	297[k] (1,2,4,7,8-) 320[k] (1,3,4,7,8-)

TABLE 1-3 (cont.)

Compound (Molecular Weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure[a] (mm Hg)	K_{oc}	UV Absorption Spectra
Pentabromodibenzofuran $C_{12}H_3Br_5O$ (562.68)	NA	NA	NA	NA	NA	NA
Hexachlorodibenzofuran $C_{12}H_2Cl_6O$ (374.87)	247-249[j] (1,2,4,6,8,9-)	NA	NA	NA	NA	NA
Hexabromodibenzofuran $C_{12}H_2Br_6O$ (641.57)	NA	NA	NA	NA	NA	NA
Octachlorodibenzofuran $C_{12}Cl_8O$ (443.76)	NA	NA	12.54-13.93[d,e]	[0.19x10^{-6}][k]	NA	NA
Octabromodibenzofuran $C_{12}OBr_8$ (799.36)	NA	NA	NA	NA	NA	NA

[a]Numbers within brackets are estimated.

[b]Berlstein, 1967

[c]Lu et al., 1979

[d]Sarna et al., 1984

[e]Webster et al., 1984

[f]Weast, 1979

[g]Coffey, 1973

[h]The numbers in parentheses represent the specific isomeric form of the compound.

[i]Gilman and Young, 1934

[j]Norström et al., 1979

[k]Firestone, 1977

[l]Crosby et al., 1973

[m]Gray et al., 1976

NA - Not available

In other words, the isomeric chlorodibenzo-p-dioxins, such as 2,3- and 2,8-dichlorodibenzo-p-dioxin have similar vapor pressures. No aqueous solubility data for tetrachlorodibenzofuran is reported (see Table 1-3); however, according to Greenlee and Poland (1978), 2,3,7,8-tetrachlorodibenzofuran is slightly more soluble in water than the corresponding dibenzo-p-dioxin, 2,3,7,8-TCDD.

Data needed for environmental fate modeling are limited for the brominated dibenzo-p-dioxins and almost nonexistent for the dibenzofurans (see Tables 1-2 and 1-3). This is consistent with the fact that none of these compounds are manufactured commercially, nor have they been detected in any commerical products or any environmental samples (U.S. EPA, 1985a). In order to establish the possible trends in the physical properties of these compounds relative to the extent of substitution, the closely related chlorinated compounds are also listed (see Tables 1-2 and 1-3). It can be concluded that water solubility, K_{ow}, K_{oc} and UV absorption spectra and BCF values increase with the increase in chlorine substitution on dibenzo-p-dioxin ring, while the vapor pressure values follow the reverse trend (see Table 1-2). The trend in increase in melting point with increase in molecular weight is generally observed, but there are a few exceptions. For example, the melting point of 2,3,7,8-tetrachlorodibenzo-p-dioxin is higher than the melting points of penta- and hexa-chloro isomers (see Table 1-2). It also appears that the 2,3,7,8-substituted tetra- and penta-chlorodibenzo-p-dioxin isomers have higher melting points than tetra- and penta-isomers not having substitutions at these positions. Extreme caution, however, should be exercised in making any conclusions with limited data, particularly since there is a 10-fold difference in the two experimental values reported for the solubility of 2,3,7,8-TCDD (see Table 1-2). The general

trend of increases in values in physical parameters with increases in chlorine substitution observed for chlorinated dibenzo-p-dioxins is also observed for chlorine-substituted dibenzofurans, although there are fewer available data for substituted dibenzofurans.

In order to further study the trend of increasing values for physical properties with increases in the number of bromine substitutions, other bromine-substituted compounds structurally-related to dibenzo-p-dioxin and dibenzofuran were studied. Other halogenated aromatic compounds, structurally-related to polyhalogenated dibenzo-p-dioxins and polyhalogenated dibenzofurans include polyhalogenated biphenyls, biphenyl ethers and naphthalenes (Mamantov, 1984). Polyhalogenated benzenes have also been included in this study because chlorinated benzenes correlate well with PCDD and PCDF (Öberg and Bergström, 1985) and more data on brominated benzenes may be available than for other similar compounds. The physical properties and BCFs in aquatic organisms for halogenated benzenes, naphthalenes, biphenyls and biphenyl ethers are given in Tables 1-4, 1-5, 1-6 and 1-7. As can be seen from Table 1-5 and Table 1-7, limited data are available for brominated naphthalenes and diphenyl ethers. Relatively more data are available for both brominated benzenes and biphenyls. These data confirm the previous conclusions based on chlorinated dibenzo-p-dioxins and dibenzofurans that water solubility, K_{ow} and K_{oc} values increase as the number of bromine substitutions increases. K_{ow} and K_{oc} values (see Tables 1-4 and 1-6) are slightly higher and vapor pressure values slightly lower for brominated compounds than the corresponding chlorinated isomers. As expected, the water solubilities for the brominated isomers are generally lower than the corresponding chlorinated isomers. There may be exceptions to this generalization as can be seen from the solubility data for hexachloro- and

TABLE 1-4

Physical Properties and BCFs of Brominated and Chlorinated Benzenes*

Compound (Molecular weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure (mm Hg)	K_{oc}	BCF
Benzene C_6H_6 (78.11)	80.1	1780 at 20°C	2.13	76 at 20°C	NA	3.5-40
Chlorobenzene C_6H_5Cl (112.56)	132	498 at 25°C	2.83-2.98	8.8 at 20°C 11.8 at 25°C	126-537	12-450
Bromobenzene C_6H_5Br (157.03)	156	360 at 25°C	2.99-3.01	3.3 at 20°C	151-631	NA
Dichlorobenzene $C_6H_4Cl_2$ (147.011)	172-181	31-100 at 20-25°C	3.38-3.59	1.0-1.9 at 25°C	170-1259	15-890
Dibromobenzene $C_6H_4Br_2$ (235.92)	218-225	20-98 at 25°C	3.64-3.79	0.24-0.43 at 25°C	NA	600
Trichlorobenzene $C_6H_3Cl_3$ (181.46)	208-219	4.1-461 at 20-25°C	3.98-4.31	0.07-0.29 at 25°C	501-2630	2300-3700
Tribromobenzene $C_6H_3Br_3$ (314.82)	271-275	2.9-200 at 25°C	4.50-6.09	NA	NA	182-12,000
Tetrachlorobenzene $C_6H_2Cl_4$ (215.90)	246-254	0.3-12.2 at 20-25°C	4.51-5.05	0.04-0.07 at 25°C	1585-3066	1800-13,000
Tetrabromobenzene $C_6H_2Br_4$ (393.72)	329	0.04 at 25°C	5.10-5.13	NA	NA	1390-6400
Pentachlorobenzene C_6HCl_5 (250.34)	275-277	0.24-0.83 at 22°C	5.03-5.79	1 at 98.6°C	3162	3400-20,000
Pentabromobenzene C_6HBr_5 (472.62)	sublimes	NA	NA	NA	NA	NA
Hexachlorobenzene C_6Cl_6 (284.76)	322-326	0.005-0.11 at 24°C	5.44-6.53	1.089×10^{-5} at 20°C	3890-38,000	5500-44,437
Hexabromobenzene C_6Br_6 (551.52)	327	NA	7.3	NA	NA	1-1100

*Sources: Horvath, 1982; Weast, 1980; Verschueren, 1983; U.S. EPA, 1984a,d; Miller et al., 1984, 1985; Sarna et al., 1984; Oliver and Niimi, 1984, 1985; Chiou, 1985; Briggs, 1981; Sabljic, 1984; Geyer et al., 1984

NA = Not available

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TABLE 1-5

Physical Properties and BCFs of Brominated and Chlorinated Naphthalenes*

Compound (Molecular weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure (mm Hg)	K_{oc}	BCF
Naphthalene $C_{10}H_8$ (128.16)	80	30.6-31.7	3.30-3.36	1 at 53°C	3.11	100-700
Chloronaphthalene $C_{10}H_7Cl$ (162.61)	-2.3 to 61	6.74-19.1	4.08-4.12	~600 at 250°C 0.017 at 20°C	NA	NA
Bromonaphthalene $C_{10}H_2Br$ (207.07)	25-54	8.2-9.9	4.35	NA	NA	NA
Dichloronaphthalene $C_{10}H_6Cl_2$ (197.06)	37-138	NA	NA	380 at 250°C	NA	NA
Dibromonaphthalene $C_{10}H_6Br_2$ (285.97)	NA	NA	NA	NA	NA	NA
Tetrachloronaphthalene $C_{10}H_4Cl_4$ (265.95)	111-198	NA	5.5	60-80 at 250°C	NA	5100
Tetrabromonaphthalene $C_{10}H_4Br_4$ (443.76)	259-261	NA	NA	NA	NA	NA
Hexachloronaphthalene $C_{10}H_2Cl_6$ (334.84)	194	NA	NA	7-10 at 250°C	NA	NA
Hexabromonaphthalene $C_{10}H_2Br_6$ (601.55)	252-269	NA	NA	NA	NA	NA
Octachloronaphthalene $C_{10}Cl_8$ (403.73)	197.5-198	NA	6.5	1.3 at 250°C	NA	330
Octabromonaphthalene $C_{10}Br_8$ (759.34)	NA	NA	NA	NA	NA	NA

*Sources: McKinney et al., 1981; Sabljic, 1984; Briggs, 1981; Oliver and Niimi, 1985; Yalkowsky et al., 1983; Verschueren, 1983; Geyer et al., 1984; MacKay and Shui, 1981; Callahan et al., 1979; U.S. EPA, 1973

NA = Not available

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TABLE 1-6

Physical Properties and BCFs of Brominated and Chlorinated Biphenyls*

Compound (Molecular weight)	Melting Point (°C)	Water Solubility (mg/ℓ)	Log K_{ow}	Vapor Pressure (mm Hg)	K_{oc}	BCF
Biphenyl $C_{12}H_{10}$ (154.20)	254	6.7-7.2	3.74-4.10	NA	NA	NA
Chlorobiphenyl $C_{12}H_9Cl$ (188.66)	282	0.8-5.8	3.90-4.80	$2.8x10^{-3}$ at 25°C	1698	890-5250
Bromobiphenyl $C_{12}H_9Br$ (233.12)	NA	0.75	4.83	NA	NA	NA
Dichlorobiphenyl $C_{12}H_8Cl_2$ (223.1)	315-319	0.067-1.94	3.55-5.58	$2x10^{-4}$ at 25°C	1700-7940	4790-80,810
Dibromobiphenyl $C_{12}H_8Br_2$ (312.03)	NA	NA	5.78	NA	NA	NA
Tetrachlorobiphenyl $C_{12}H_6Cl_4$ (292.0)	NA	11-175 µg/ℓ	4.63-6.85	$1.9-5.5x10^{-5}$ at 25°C	46,770	460-48,980
Tetrabromobiphenyl $C_{12}H_6Br_4$ (469.7)	NA	NA	7.41	NA	NA	470
Hexachlorobiphenyl $C_{12}H_4Cl_6$ (360.9)	NA	0.2-6.0 µg/ℓ	6.51-8.26	$1.2x10^{-5}$ at 25°C	112,200	4800-1,202,260
Hexabromobiphenyl $C_{12}H_4Br_6$ (627.4)	NA	11 µg/kg	NA	$7.6x10^{-5}$ at 90°C	NA	NA
Octachlorobiphenyl $C_{12}H_2Cl_8$ (429.7)	NA	0.18-1.39 µg/ℓ	7.11-9.69	$7.6x10^{-6}$ at 25°C	NA	NA
Octabromobiphenyl $C_{12}H_2Br_8$ (785.2)	NA	20-30 µg/kg	NA	NA	NA	NA
Decachlorobiphenyl $C_{12}Cl_{10}$ (498.5)	NA	0.007-0.49 µg/ℓ	8.26-11.20	$4.0x10^{-10}$ at 25°C	NA	97,720-933,250
Decabromobiphenyl $C_{12}Br_{10}$ (943.1)	NA	NA	NA	NA	NA	NA

*Sources: Yalkowsky et al., 1983; IARC, 1978; Verschueren, 1983; McFarland et al., 1984; Rapaport and Eisenreich, 1984; Leifer et al., 1983; Miller et al., 1984, 1985; Woodburn et al., 1984; Sarna et al., 1984; Oliver and Niimi, 1985; Sugiura et al., 1978; MacKay and Hughes, 1984; Chiou, 1985; Sabljic, 1984

NA = Not available

TABLE 1-7

Physical Properties and BCFs of Brominated and Chlorinated Diphenyl Ethers*

Compound (Molecular weight)	Melting Point (°C)	Water Solubility	Log K_{ow}	Vapor Pressure (mm Hg)	K_{oc}	BCF
Diphenyl ether $C_{12}H_{10}O$ (170.20	257-259	21 mg/ℓ at 25°C	4.20	0.02 at 25°C	NA	195
Chlorodiphenyl ether $C_{12}H_9OCl$ (204.65)	NA	NA	4.25	NA	NA	NA
Bromodiphenyl ether $C_{12}H_9OBr$ (249.11)	310.1	NA	4.28	1.13	NA	NA
Dichlorodiphenyl ether $C_{12}H_8OCl_2$ (239.10)	NA	NA	4.82-5.52	NA	NA	9300
Dibromodiphenyl ether $C_{12}H_8OBr_2$ (328.02)	338-340	NA	NA	NA	NA	NA
Tetrachlorodiphenyl ether $C_{12}H_6OCl_4$ (307.99)	NA	NA	6.55	NA	NA	NA
Tetrabromodiphenyl ether $C_{12}H_6OBr_4$ (485.82)	NA	NA	NA	NA	NA	NA
Decachlorodiphenyl ether $C_{12}OCl_{10}$ (514.66)	NA	NA	12.24	NA	NA	NA
Decabromodiphenyl ether $C_{12}OBr_{10}$ (959.17)	290-306	20-30 µg/ℓ	NA	<1 at 250°C	NA	NA

*Sources: Webster et al., 1984; U.S. EPA, 1984b; Oliver and Niimi, 1984

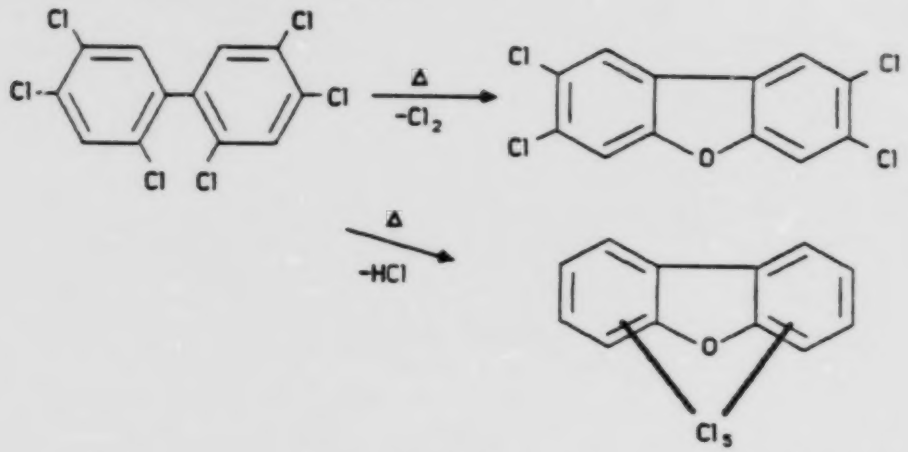
NA - Not available

hexabromo-biphenyl and octachloro- and octabromo-biphenyl pairs (see Table 1-6). It appears that both hexabromo- and octabromobiphenyls have higher solubilities than the corresponding chlorinated isomers (see Table 1-6). Since the solubility data were measured by different investigators (IARC, 1978; Yalkowsky et al., 1983) and different methods were used to obtain the data, it is unclear whether the different methods could cause a large variation in reported solubility values as has been observed with two experimental values for 2,3,7,8-tetrachlorodibenzo-p-dioxin (see Table 1-2). Fulvic acid, however, will increase the aqueous solubility of 1,2,3,4,7-penta-chlorodibenzo-p-dioxin (Webster et al., 1984). Therefore, introduction of dissolved organic matter functions may enhance the solubilities of other PCDDs. The general pattern of increase in K_{ow} and K_{oc} values and a decrease in vapor pressure and solubility values with the increase in the number of halogen substitutions may not follow in the case of BCFs in aquatic organisms. Suguira et al. (1978) reported that BCFs for chloro- and bromobiphenyls are proportional to K_{ow} up to a K_{ow} of 10^6. At higher K_{ow}s, BCF values become lower than the value expected from a linear correlation. Similarly, the BCF in the case of chlorinated benzenes increased with increasing number of chlorine substitutions (see Table 1-4). This correlation, however, may not apply to PBBs (see Table 1-4). The U.S. EPA (1984a) reported that hexabromobenzene, unlike hexachlorobenzene, did not significantly bioaccumulate in juvenile Atlantic salmon, Salmo salar, or in carp, Cyprinus carpus. Therefore, the bioaccumulative properties of chlorinated benzenes may not accurately predict the bioaccumulation of the analogous bromobenzenes.

1.2. SOURCES IN THE ENVIRONMENT

When pyrolyzed at 380-400°C in open glass tubes, 50 mg of the PBB fire retardant, Fire Master FF-1, the principal compound of which is 2,2',4,4',5,5'-hexabromobiphenyl (Pomerantz et al., 1978; Buser et al., 1978) produced both 2,3,7,8-tetrabromodibenzofuran (40 ppm) and pentabrominated dibenzofurans (4 ppm) (O'Keefe, 1978). Pyrolysis of Fire Master FF-1 under nitrogen in sealed tubes also produced trace amounts of tetrabrominated dibenzofurans (O'Keefe, 1978). Similarly, Buser et al. (1978) reported the detection of 2,3,7,8-tetrabromodibenzofuran as a product of pyrolysis of Fire Master BP-6 at 600°C in the presence of air. Therefore, any operation involving the pyrolysis of PBBs is likely to be a source of brominated dibenzofurans in the environment. Two such operations are incineration involving materials containing this fire retardant and the production process for PBBs. This conclusion is based not only on the results of pyrolysis of PBBs but also on the results of experiments with the structurally similar PCBs. The pyrolysis of 2,4,5,2',4',5'-hexachlorobiphenyl between temperatures of 550 and <700°C produced 2,3,7,8-tetrachlorodibenzofuran and 2-pentachlorodibenzofuran isomers. Pyrolysis of 2,4,6,2'4'6'-hexachlorobiphenyl, on the other hand, produced 1,3,7,9-tetrachlorodibenzofuran and 1-pentachlorodibenzofuran isomers (Buser et al., 1978). At temperatures >700°C, complete destruction of the PCDF occurred. No di-, tri- or hexachlorinated dibenzofurans were obtained at any of these temperatures (Buser et al., 1978). The pyrolysis of Aroclor 1254 containing tri-, tetra-, penta- and hexachlorinated biphenyls as the major components produced mono-, di-, tri-, tetra- and pentachlorinated dibenzofurans.

Again, at pyrolysis temperatures of >700°C, all the chlorinated dibenzofurans decomposed (Buser et al., 1978). The proposed mechanisms for the formation of tetra- and pentachlorodibenzofurans from hexachlorobiphenyls are as follows (Buser et al., 1978):



The most recent example of the formation of PCDD and PCDF during the pyrolysis of PCBs and chlorobenzenes is the accidental fire involving PCB- and chlorobenzene-containing transformers in an office building in Binghamton, NY (Schecter and Tiernan, 1985; Schecter et al., 1985).

PCDFs are often found as contaminants in PCBs (Smith et al., 1984; Czuczwa and Hites, 1984). Buser et al. (1978) reported that the concentration of PCDFs as impurities in commercial PCBs from Europe, the United States and Japan are in the ppm level. By analogy, it is suspected that commercial PBBs will contain brominated dibenzofurans as impurities, although PBBs are not exposed to the high temperatures that PCBs are in capacitor and transformer applications. Brominated dibenzofurans have not been reported in commercial PBB mixtures (Pomerantz et al., 1978). The failure to use suitable analytical methods with low detection limits may be the reason why these compounds have not been detected earlier in PBBs.

In order to assess the potential sources of PBDDs in the environment, it is necessary to study the sources of PCDDs, structurally-similar and more thoroughly studied compounds. Possible sources of PCDDs in the environment have been reviewed in U.S. EPA (1980a, 1985b). Briefly, the sources of PCDD in the environment can be categorized into five groups: industrial processes, municipal incinerations, chemical dump sites, photochemical processes and other combustion processes. The production of PCDDs during the manufacturing processes involving chlorophenols and its derivatives are well-documented (U.S. EPA, 1985b). 2,3,7,8-TCDD contamination as high as 30 ppm was reported in 2,4,5-T that was manufactured before 1970 (Hussain et al., 1972). Efforts were made during the 1970s to control and minimize the formation of 2,3,7,8-TCDD in chlorophenol derivatives such as 2,4,5-T and hexachlorophenol, and as a result, all the products manufactured during the later 1970s were claimed to have contained <0.1 μg/g 2,3,7,8-TCDD (U.S. EPA, 1985b). The chlorophenols and its derivatives that were found to contain PCDDs are o-chlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, pentachlorophenol, 2,4-D, 2,4,5-T, Silvex, Agent Orange, Agent Purple and hexachlorophene (U.S. EPA, 1985b). The presence of 2,3,7,8-TCDD in 2,4-D due to contamination of manufacturing equipment has also been reported (U.S. EPA, 1985b). Since trichlorophenol is used in the production of diphenyl ether herbicides, PCDDs have been detected in these herbicides as well (U.S. EPA, 1985b). Commercial pentachlorophenol contains relatively high levels of hexa-, hepta- and octa-CDDs and essentially no 2,3,7,8-TCDD (Smith et al., 1984). Finally, incineration of selected industrial waste containing chlorinated precursors in industrial boilers are likely sources of industrially produced PCDDs in the environment (U.S. EPA, 1985b). The highly toxic 1,2,3,7,8-penta CDD is a major PCDD in the incineration products of PCP (Smith et al., 1984).

Examples of how PCDD can be formed during the manufacture of chlorophenols are given in Figure 1-1. These examples show that the number of chlorine substituents in the major contaminant will be (n-1)x2 where n is the number of chlorines in the starting chlorophenol. Consequently, dichlorodibenzo-p-dioxin is expected to be the major contaminant from dichlorophenol, TCDD from trichlorophenol and hexachlorodibenzo-p-dioxin from tetrachlorophenol.

It has been reported that ~12,000 metric tons/year of hazardous wastes were produced in the manufacture of chlorophenols, and ~80,000 metric tons/year in the manufacture of phenoxy herbicides (U.S. EPA, 1985b). Some of the these wastes entered waste disposal sites, causing contamination of these sites. The contaminations of waste disposal sites in Love Canal, NY, Jacksonville, AR, and horse breeding areas in eastern Missouri sprayed with waste oil are well-documented (U.S. EPA, 1985b). The most recent incident of PCDD contamination was a dumpsite near Times Beach, MI.

The formation of PCDDs including 2,3,7,8-TCDD from a variety of municipal incinerators in Canada, Europe and the United States has been demonstrated (U.S. EPA, 1985b); however, a fundamental point of debate about the production of PCDD and PCDF during municipal incineration is whether these compounds are formed by the cyclization of chlorinated precursors (such as chlorophenols and chlorobenzenes) present in the fuel or by the reaction of organic compounds with inorganic chlorine present in the fuel. Recent investigations indicate that the first mechanism is likely to produce the majority of PCDF and PCDD during municipal incineration (Czuczwa and Hites, 1984). From the analysis of dated sediment cores from Lake Huron, Czuczwa and Hites (1984) concluded that precipitated PCDDs and PCDFs from airborne particles formed during municipal and industrial incineration are the main sources of these compounds in lake sediments.

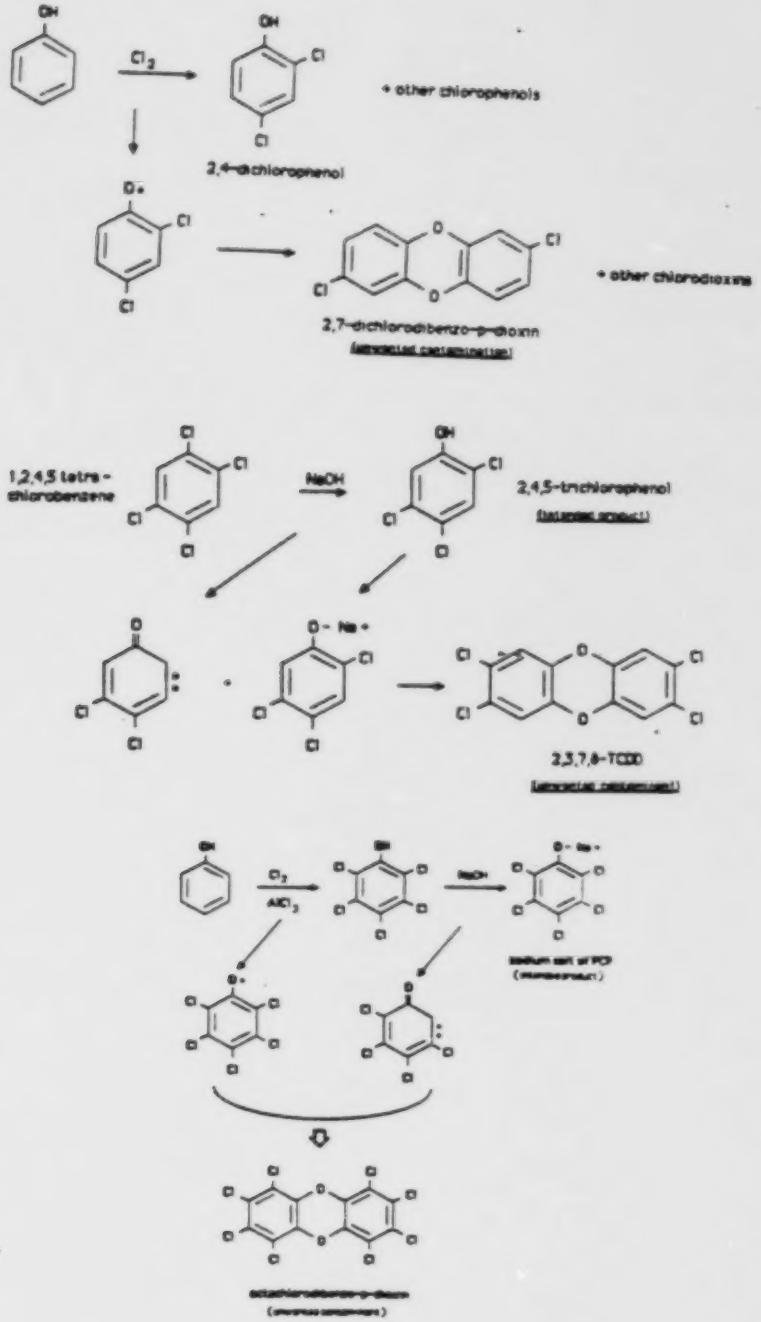


FIGURE 1-1

Examples of the Formation of Selected PCDDs During Manufacture of Chlorophenols

Source: U.S. EPA, 1980a

Photochemical processes can also lead to the formation of PCDDs. The photolysis of PCP-treated woods may lead to the formation of PCDDs (U.S. EPA, 1985b). Other photolysis processes involving the possibility of formation of lower congeners of PCDDs from the photolysis of higher congeners have been discussed in U.S. EPA (1985b).

The formation of PCDDs from combustion sources not requiring the presence of chlorinated organic precursors (such as chlorobenzenes, chlorophenols and PCB) was postulated in U.S. EPA (1985b). These investigators claimed to have detected PCDDs from mufflers of diesel trucks and passenger vehicles, woodburning fireplaces and cigarette smoke; however, there is little experimental evidence to support that, with the exception of octa- and hepta-CDDs, other PCDDs and PCDFs are formed by reaction of organic compounds with inorganic chlorine present in the fuel (U.S. EPA, 1985b; Czuczwa and Hites, 1984).

Drawing an analogy from PCDDs, it can be speculated that brominated phenols, biphenyls and diphenyls, ethers and benzenes, as well as other brominated organics, may produce PBDDs as contaminants during production (depending on the method of synthesis), pyrolysis or incineration. Evidence of the formation of PBDDs and PBDFs from the pyrolysis of such compounds is provided by Buser (1986) and Thoma et al. (1986). The pyrolysis of technical grade pentabromo-, octabromo- and decabromodiphenyl ether used as flame retardants produced a series of PBDDs and PBDFs at a total yield of $\leq$10% (Buser, 1986). Table 1-8 lists the PBDDs and PBDFs formed from the pyrolysis of brominated diphenyls. Although tetrabromodibenzofurans and tetrabromodibenzodioxins were detected, the presence of various isomers could not be determined because of the lack of reference compounds. The

TABLE 1-8

PBDFs and PBDDs Formed from Pyrolysis of Brominated Diphenyl Ethers[a]

Brominated Diphenyl Ether	Pyrolysis Temperature (°C)	PBDFs (F) and PBDDs (D) Formed								Total Yield of PBDFs & PBDDs (%)
		Mono-	Di-	Tri-	Tetra-	Penta-	Hexa-	Hepta-	Octa-	
Pentabromo-	510	(F)+[b]	+	+	+	+	ND	ND	ND	0.5-1
		(D)+	++	+	+	ND	ND	ND	ND	
	630	(F)+	+	++	+++	+++	+	ND	ND	10
		(D)+	+++	+++	++	+	ND	ND	ND	
Octabromo-	630	(F)ND	ND	ND	+	++	+++	+	ND	5
		(D)ND	ND	+	++	+++	++	+	ND	
Decabromo-	630	(F)ND	ND	ND	+	+	+	++	ND	1-2
		(D)ND	ND	ND	+	++	++	+	+	

[a]Source: Buser, 1986

[b]Amounts indicated semiquantitatively by number of marks (+).

ND = Not detected

only reference standard used in this study was 2,3,7,8-tetrabromodibenzofuran. Buser (1986) does not clearly specify that this compound was detected.

Similarly, the pyrolysis of purified 2,4,6-tribromophenol, pentabromophenol and tetrabromobisphenol A produced a series of PBDDs and PBDFs (Table 1-9); yet, the pyrolysis of tetrabromophthalic anhydride at 700, 800 and 900°C produced no PBDDs or PBDFs (Thoma et al., 1986). Some brominated compounds that may be related to PBDD formation along with their present U.S. manufacturers are shown in Figure 1-2 and Table 1-10.

The majority (~35% of the 350 million pounds of bromine used in 1985) of brominated organic compounds such as decabromodiphenyl oxide, tribromophenol, octabromodiphenyl oxide, tetrabromophthalic anhydride, hexabromocyclododecane, di- and tetrabromobisphenol-A are used as fire retardants in a variety of thermoplastics or in the production of fire retardant thermoplastics (for example, allyl ethers and methacrylate esters of brominated bisphenol-A and vinyl bromide) (Verbanic, 1986); it is likely that incineration of such plastics and disposal of these plastics in dumpsites may be a major source of environmental contamination from PBDDs. Other bromoorganic compounds of commercial significance are ethylene dibromide (3 4 million pounds for lead scavengers in gasoline and 20 million pounds for pesticides; the latter is currently banned), methyl bromide (40-50 millions pounds - 65% soil fumigant, 15% space fumigant, 10-15% exported) and bromofluorocarbon fire extinguishers. These latter compounds, however, are probably not good precursors of PBDDs of PBDFs.

The estimation of total PBDD contaminants generated during the production of the precursor chemicals listed above requires knowledge of the production volume of these chemicals and the amount of PBDD contamination in

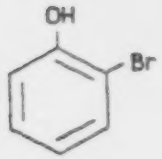
TABLE 1-9

Dibenzo-p-dioxins Formed from the Pyrolysis of Brominated Phenols*

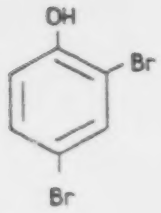
Brominated Phenol	Pyrolysis Temperature (°C)	Amounts of PBDFs (F) and PBDDs (D) Formed (ppm)							
		Mono-	Di-	Tri-	Tetra-	Penta-	Hexa-	Hepta-	Octa-
2,4,6-Tribromo-	700	(F) ND	171	1000	4180	1439	ND	ND	ND
		(D) ND	3854	31,870	186,800	3146	85	ND	ND
	800	(F) ND	ND	ND	8950	ND	ND	ND	ND
		(D) ND	ND	40,898	896,000	3053	ND	ND	ND
Pentabromo-	700	(F) ND	ND	ND	ND	12	48	132	ND
		(D) ND	ND	ND	ND	90	872	480	ND
	800	(F) ND	ND	ND	ND	ND	ND	7042	ND
		(D) ND	ND	ND	ND	375	1840	3621	1672
Tetrabromo-bisphenol A	700	(F) 77	49	6	ND	ND	ND	ND	ND
		(D) 19	32	11	1	ND	ND	ND	ND
	800	(F) 270	623	236	21	ND	ND	ND	ND
		(D) 129	233	109	27	ND	ND	ND	ND

*Source: Thoma et al., 1986

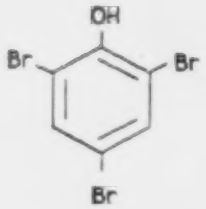
ND = Not detected



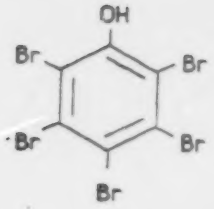
o-Bromophenol



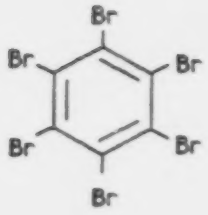
2,4-Dibromophenol



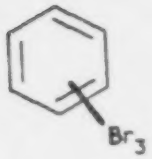
2,4,6-Tribromophenol



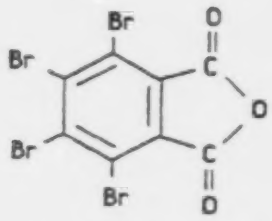
Pentabromophenol



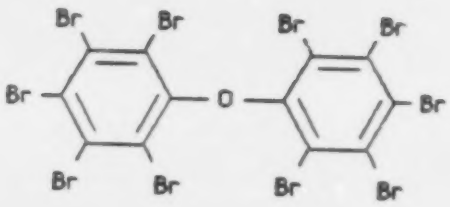
Hexabromobenzene



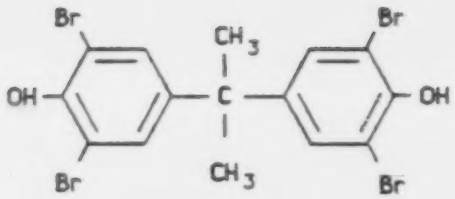
Tribromobenzene



Tetrabromophthalic anhydride



Decabromodiphenyl oxide



Tetrabromobisphenol-A

FIGURE 1-2

Brominated Compounds Related to PBDD Formation

Source: U.S. EPA, 1980a

TABLE 1-10

Current U.S. Manufacturers of Suspected Precursors of PBDDs*

Compound	Manufacturer	Location
Decabromodiphenyl oxide	Great Lakes Chemical	El Dorado, AR
	Ethyl Corporation	Magnolia, AR
	White Chemical Corporation	Newark, NJ
Pentabromophenol	Great Lakes Chemical	El Dorado, AR
2,4-Dibromophenol	Dow Chemical, U.S.A.	Midland, MI
	Great Lakes Chemical	El Dorado, AR
	White Chemical Corporation	Newark, NJ
2,4,6-Tribromophenol	United-Guardian, Inc.	Hauppauge, NY
	White Chemical Corporation	Newark, NJ
o-Bromophenol	RSA Corporation	Ardsley, NY
Tetrabromobisphenol-A	Great Lakes Chemical	El Dorado, AR
	Ethyl Corporation	Magnolia, AR
Hexabromobenzene	Velsicol Chemical	St. Louis, MO
Tribromobenzene	Diaz Chemical Corporation	Holley, NY
Tetrabromophthalic anhydride	Ethyl Corporation	Sayreville, NJ
	Great Lakes Chemical	El Dorado, AR

*Source: SRI, 1985; U.S. EPA., 1980a

each of these chemicals. Although the amount of PBDD contamination in precursor chemicals is not known, the levels of these contaminants may be similar to the impurity levels in similar chlorinated precursors. Without production volume data for the brominated precursors, however, it is not possible to estimate total PBDD produced as contaminants in bromoorganic compounds.

The sources of PCDFs in the environment are expected to be similar to those for PCDDs, which occur as contaminants in phenoxy herbicides, polychlorinated phenols, hexachlorobenzene, PCBs and polychlorinated diphenyl ethers (Pomerantz et al., 1978). Incineration of municipal and industrial wastes containing precursor compounds also produce PCDFs (Buser and Bosshardt, 1978; Buser et al., 1978). The photolysis of polyhalogenated biphenyls also produces PCDFs (Pomerantz et al., 1978). The sources of brominated dibenzofurans in the environment are likely to be similar to the corresponding chlorinated compounds; however, as in the case of polybrominated dioxins, polybrominated dibenzofurans are likely to be produced in much smaller amounts than are polychlorinated dibenzofurans.

1.3. SUMMARY

Brominated dibenzo-p-dioxins and dibenzofurans can exist in 75 and 135 possible isomeric forms, respectively; of these, only a few compounds have been prepared and characterized. Parameters, including water solubility, K_{ow}, vapor pressure, K_{oc}, light absorption characteristics and BCFs, necessary for the prediction of environmental fate and transport of these compounds, have been estimated for a few dibrominated and tetrabrominated isomers. Physical properties for structurally-related polybrominated compounds were studied to establish a general trend of increase in K_{ow} and K_{oc} and a decrease in vapor pressure and aqueous solubility as the number of halogen substitutions increased.

A likely source of PBDDs and PBDFs in the environment is pyrolysis of PBBs (Pomerantz et al., 1978; Buser et al., 1978), 2,4,6-tribromophenol, pentabromophenol, tetrabromobisphenol A (Ihoma et al., 1986) and polybrominated diphenylether (Buser, 1986). Since elevated temperatures are used during the manufacture of chemicals and the incineration of waste materials, the PBDDs and PBDFs are expected to be present in the precursor materials (for example, 2,4,6-tribromophenol) and in emissions from incineration processes involving the precursor materials. Without production volume data for the brominated precursors, it is not possible to estimate total PBDD produced as contaminants in bromoorganic compounds.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Pertinent experimental data regarding the fate and transport of PBDDs and PBDFs could not be located in the available literature. Predictions about the environmental fate and transport of these compounds can be made based on the fate and transport of the corresponding chlorinated compounds and from environmental modeling, based upon physical parameters of these compounds. There are limitations, however, for both methods. Experimental data regarding the fate and transport of PCDDs were limited and these data were almost nonexistent for PCDFs. Modeling data based upon physical parameters are approximate and in most cases do not differentiate the environmental characteristics among positional isomers. In some cases physical parameter data for the PCDDs and PCDFs were not available. Therefore, environmental fate data, based upon physical properties of other halogenated compounds structurally related to PCDDs and PCDFs listed in Section 1.2. will be used to predict the environmental fate and transport of the PBDDs and PBDFs.

In order to consider the possibility of photolysis of PBDDs and PBDFs in the atmosphere, surface water, sediments and soil, the available data on PCDDs and PCDFs will be reviewed. The photolysis of 2,3,7,8-TCDD was studied by several authors, and it was concluded that although it undergoes significant photodecomposition in the presence of H-donating media, the pure compound in distilled water or coated on glass plates remained stable (U.S. EPA, 1985b; Liberti et al., 1978). The photodegradation by a sunlamp of several PCDDs in hexadecane solution and on surfaces (glass) coated with these compounds was reported by Nestrick et al. (1980). The absolute half-lives of the PCDDs estimated by these authors are given in Table 2-1.

TABLE 2-1

Photolytic Half-Lives of PCDDs*

Chlorinated Dibenzo-p-dioxin	$t_{1/2}$ (minutes in hexadecane solution)	$t_{1/2}$ (minutes on glass surface)
2,3,7,8-tetra-CDD	56.8	8,400
1,3,6,8-tetra-CDD	15.3	160
1,3,6,8-tetra-CDD	482	264
1,4,6,9-tetra-CDD	8400	830
1,2,3,7,8-penta-CDD	456	52.8
1,2,3,6,7,8-hexa-CDD	379	44,100
1,2,3,6,6,9-hexa-CDD	764	NA
1,2,3,4,6,7,8-hepta-CDD	1800	3,140
1,2,3,6,7,9-hepta-CDD	3300	2,400

*Source: Nestrick et al., 1980

NA = Not available

It can be concluded that the photodecomposition rate of PCDDs are dependent both on photolytic media and on the nature of the isomer (see Table 2-1). Thus, the different isomers of tetra-, hexa- and hepta-CDDs listed in Table 2-1 have widely different photodecomposition half-lives; the trend in half-lives pattern changed when the photolytic medium was changed. 1,4,6,9-Tetra-CDD, which showed the longest half-life in hexadecane solution, did not show the longest half-life when irradiated on the glass surface. Thus, the nature of the surface is also important for the photolysis of PCDD (Liberti et al., 1978). The photodecomposition of TCDD was found to be substantial on silica gel and alumina, but the reaction was insignificant on glass or marble (Liberti et al., 1978).

The photolysis of PCDDs in an organic solvent capable of donating H to the reaction intermediate does not represent PCDD photolysis conditions in surface waters. There is a possibility of 2,3,7,8-TCDD photolysis in outdoor pond water (U.S. EPA, 1985b). The fate of 1,3,6,8-tetra-CDD in an outdoor aquatic system was studied by Corbet et al. (1983). Filtered and autoclaved pond water protected from sunlight lost only 20% of ^{14}C-1,3,6,8-tetra-CDD, whereas the loss was 62% for autoclaved water exposed to 28 days of sunlight (i.e., 42% of the compound photodegraded in 28 days). The photodegradation of 1,2,3,4,7-penta-CDD and 1,2,3,4,7,8-hexa-CDD in aqueous solution was reported by Choudhry and Webster (1985), who estimated that the typical photolytic half-lives of 1,2,3,4,7-penta- and 1,2,3,4,7,8-hexa-CDD near the surface of bodies of water at 40° N latitude would be 15-52 days and 6-22 days, respectively. (Decomposition was higher in summer than in winter.) In actual surface waters, the partitioning of PCDD in water and suspended particles, the light scattering effect of these particles and the depth of the body of water will all contribute to the increase of photolytic half-lives reported by Choudhry and Webster (1985).

It can be concluded from this study and the study of Nestrick et al. (1980), however, that the photolysis rate may not necessarily decrease with an increase in chlorine substitution and that PCDD with 2,3,7,8-substitution may undergo faster photodegradation than substituents in other positions of the ring.

The photodegradation of 2,3,7,8-TCDD on wet and dry soil surfaces was found to be negligible (Liberti et al., 1978; Kearney et al., 1973; U.S. EPA, 1985b). The available data regarding the photodegradation of particle sorbed PCDD in the atmosphere are conflicting. While the earlier investigators found negligible photodegradation with sunlight, more recent work indicates that atmospheric PCDD may undergo some photolysis (U.S. EPA, 1985b).

Laboratory studies on the photolysis of PCDFs also showed similar results. The photodegradation was found to be solvent-dependent and proceeded faster in media where H-donators are more easily available. The photodegradation proceeded mainly through reductive dechlorination; however, there is a major difference between the photolytic processes in PCDFs and PCDDs. Whereas in PCDDs, the photodegradation rate generally decreases as the chlorine substitution increases, the reverse may be true for PCDFs. Thus, dichlorodibenzofuran was found to have a slower photodegradation rate than octachlorodibenzofuran (Hutzinger, 1972; Hutzinger et al., 1973). No model aquatic fate study on the photodegradability of PCDFs was located in the available literature.

The loss of 2,3,7,8-TCDD in aquatic systems and soil as a result of biodegradation has been investigated by several authors (U.S. EPA, 1985b).

The estimated biodegradation half-life of 2,3,7,8-TCDD in aquatic systems is >1 year and in soil, 10-12 years (U.S. EPA, 1985b). Czuczwa and Hites (1984) found no evidence of degradation of PCDDs or PCDFs in sediment cores in Lake Huron.

The volatilization of 2,3,7,8-TCDD from water was not directly studied by earlier investigators, but several authors implicated volatilization as one of the major reasons for the unaccounted for disappearance of this compound from aqueous solutions during microbial studies. More recent outdoor pond studies (Corbet et al., 1983; Marcheterre et al., 1985) with spiked 1,3,6,8-TCDD and octa-CDD provide evidence that volatilization was a significant process for the loss of both compounds from the experimental pond, although no quantitative data on volatilization rate were provided. Both experiments showed that volatilization loss was greatest during the first day after treatment. A comparison of the two experiments shows that volatilization loss from water may be slightly higher for 1,3,6,8-TCDD than octa-CDD. Based on the environmental fate modeling of chloro-CDDs, Webster et al. (1985) came to the same conclusions; that is, PCDDs will volatilize significantly from aquatic systems and that higher chlorinated congeners may have lower volatility than lower chlorinated congeners.

Another important process that may dictate the fate of PCDDs in air, water and soil is sorption. Several recent investigations (Tsushimoto et al., 1982a; Corbet et al., 1983; Marcheterre et al., 1985) have provided evidence that distributions in the sediment (through sorption) and aquatic plants and animals are an important sink for aquatic PCDDs. Table 2-2 lists the percent distribution of 1,3,6,8-TCDD applied to an outdoor experimental pond at different times after application; sediment and aquatic organisms are the primary sinks for aquatic TCDD.

TABLE 2-2

Percent Distribution 1,3,6,8-TCDD in Different Compartments of the Aquatic System*

Compartment	Time (days)					
	0	1.0	4.0	8.0	34	90
Water	100	8.3	1.4	0.68	0.12	0.15
Sediment (extractable, nonextractable)	0	30	54.9	45.2	71.1	19.3
Vegetation	0	ND	ND	5.8	2.5	2.4
Fish (fathead minnow)	0	0.34	0.44	0.36	NA	NA
Snails	0	NR	1.8-2.1	NR	NR	NR

*Source: Corbet et al., 1983

ND = Not detected; NR = not reported; NA = not applicable

Similarly, it has been demonstrated that TCDD will be strongly sorbed to soil and that vertical movement of TCDD in soils will be negligible (U.S. EPA, 1985b; Kearney et al., 1971). Transport of PCDD may occur by horizontal transfer (eroded soil transported by water) and through contaminated airborne dust particles. Because of this strong sorption to soil, PCDDs are unlikely to leach into groundwater under normal conditions; however, some leaching from soil is possible after multiple application or accidental release of PCDD to soil (U.S. EPA, 1985b).

Small quantities of 2,3,7,8-TCDD (<40 ppb) were accumulated in young oat and soybean plants grown on a sandy loam soil contaminated with this compound (60 ppb) (Kearney et al., 1973). Neither mature plants nor seeds of these plants showed the presence of 2,3,7,8-TCDD (<1 ppb). The compound was not translocated from leaf surfaces to other plant parts.

Based on the limited experimental data on the fate and transport of PCDDs and PCDFs and fate modeling from their physical properties, some qualitative predictions about the fate and transport of the corresponding brominated compounds can be made. Bromine, however, is a better leaving group than chlorine in most chemical reactions. Laboratory experiments on the alkaline hydrolysis and photolysis of PBB show that bromine is more labile than chlorine under comparable reaction conditions (Pomerantz et al., 1978). In addition, prediction of photochemical reactivity and biodegradability is particularly risky. Although the PBDDs and PBDFs absorb sunlight (>290 nm; see Table 1-2), whether they will use the light energy in photodegradation reactions in a similar manner to one of chlorinated analogs is unknown. In general, the biodegradability of halogenated aromatic compounds decreases as the number of halogens increases. The available data on the

PCDDs and PCDFs suggest that this is also true for halogenated dibenzofurans, but may not be true for the brominated analogs if some microorganisms have the required enzymes for biodegradation. In contrast, analogies between the chlorinated and brominated analogs for transport processes are probably fairly accurate because many of the processes correlate well with physical properties, which are similar for the chlorinated and brominated analogs.

In the atmosphere, PBDDs and PBDFs are likely to be present predominantly in the particle-sorbed states. Some photolysis of these compounds may occur in the atmosphere, although adsorption to particulate matter appears to provide some stability. Substantial amounts of the atmospheric PBDDs and PBDFs will precipitate on land and particularly in surface waters. By analogy with chlorinated biphenyls (Kotzias et al., 1979), the higher substituted PBDDs may photodegrade slower than lower substituted PBDDs. In the case of brominated dibenzofurans, octa-substituted compounds may photolyze faster. The predominance of hepta-, penta- and tetra-CDFs in Lake Huron sediment samples indicate that the corresponding brominated compound may also be less susceptible to photodegradation than the octa-isomer.

In aqueous media, the brominated compounds are expected to have long lifetimes. By analogy to PCDDs, the biodegradation rates of the corresponding brominated compounds are expected to be slow. Since the biodegradation rate decreases with an increase in the number of chlorine substitutions for chlorinated biphenyls (Bailey et al., 1983; Fries and Marrow, 1984; Isbister et al., 1984), similar trends in biodegradation for higher substituted PCDDs and PBDDs and PBDFs are expected. Under simulated natural conditions, monobrominated biphenyls biodegraded at a slightly faster rate than monochlorinated biphenyls (Kong and Sayler, 1983). Therefore, the biodegradation rate

for PBDDs and PBDFs may be faster than the corresponding chlorinated compounds. Biodegradation, nonetheless, is not expected to be a significant process for PBDDs and PBDFs. Some of the brominated compounds will undergo volatilization and photolysis, but most compounds are expected to be adsorbed by sediments or taken up by aquatic organisms. By analogy to the chlorinated compounds, the brominated compounds will probably undergo very slow biodegradation in the sediments. In aquatic organisms, these compounds will undergo substantial bioaccumulation. Compounds with high K_{ow} values (for example, K_{ow} of $>10^6$), however, may not bioaccumulate proportionally with the predicted correlation equations. The sorption of these compounds to sediments is expected to increase with increased bromine substitution and the volatilization is expected to follow the reverse trend.

In soil, the biodegradation of both brominated dioxins and furans is suspected to be very slow. Both classes of compounds are expected to be sorbed strongly to soil and remain essentially immobile there. The degree of sorption may increase with the increase in bromine substitution to the parent compound. Under normal conditions, none of these compounds will leach from soil to groundwater. Transport of these compounds from soil to surface water may occur through eroded soil transported by runoff water and from soil to the atmosphere through contaminated airborne dust particles.

No experimental data on the fate and transport of these compounds in the environment are available. Based on the limited data available for the polychlorinated compounds and fate modeling from the physical properties of the polybrominated compounds, some speculations about their fate and transport in the environment have been made. Generally, the persistence of polybrominated compounds in different environmental media is increased with an increase in bromine substitution. In air, these compounds may be removed

by slow photodegradation, and dry and wet deposition, but are expected to be persistent in the atmosphere. In water, the PBDDs and PBDFs may undergo slow photolysis, biodegradation, volatilization and a strong sorption onto suspended particulates and sediments, and are expected to persist in water as well. These compounds will undergo substantial bioaccumulation in aquatic organisms. In soils, they are also expected to be persistent, strongly sorbing to soil and remaining essentially immobile there. Under normal conditions, none of these compounds will leach to groundwater. Transport may occur from soil to surface water by runoff water and from soil to the atmosphere through airborne dust particles.

3. ENVIRONMENTAL LEVELS

No PBDDs and PBDFs have ever been detected in air, water, soil or any other environmental samples.

The complete absence of monitoring data may reflect the lack of effort made to identify and quantify these compounds in the environments where they may occur, such as contaminants in brominated fire retardants and in the emissions from the incinerations of these products. The probability of producing significant quantities of brominated dibenzofurans and dibenzo-p-dioxins is much lower than the corresponding chlorinated analogues because of the low production volume of the brominated precursors. In addition, the nonavailability of authentic reference compounds makes absolute identification of these compounds impossible. These factors may contribute to the lack of efforts made for the identification and quantification of these compounds.

4. PHARMACOKINETICS

Few reports were located in which the pharmacokinetics of homologous brominated and chlorinated congeners of halogenated aromatic hydrocarbons were compared. Available data regarding the brominated dibenzo-p-dioxins and dibenzofurans were extremely limited. The pharmacokinetics of the PCBs, however, has been studied exhaustively, and these studies provide the primary bases for generalizations on other halogenated aromatic hydrocarbons.

4.1. ABSORPTION

Relevant data were located only regarding absorption of the halogenated aromatic hydrocarbons following oral exposure. Gastrointestinal absorption of the halogenated aromatic hydrocarbons occurs by diffusion and is expected to be rapid and efficient because of the lipophilicity of these compounds, as indicated by their log p values (Birnbaum, 1985). Generally, log p increases within a class of aromatic hydrocarbon with increasing halogenation. The gastrointestinal absorption of several PCB congeners including 2,4,5,2',4',5'-PCB appears to be $\geq$90% of an orally administered dose in rats (Albro and Fishbein, 1972; Matthews and Anderson, 1975a) and mice (Morales et al., 1979), regardless of extent or position of halogenation. Gastrointestinal absorption $\geq$90% was also observed for 2,4,5,2',4',5'-PBB in rats (Matthews et al., 1977; Tuey and Matthews, 1980), indicating similar gastrointestinal absorption of the 2,4,5,2',4',5'-chlorinated and brominated biphenyls.

The extent of gastrointestinal absorption of the halogenated benzenes is influenced by the extent of halogenation (U.S. EPA, 1977). Monochloro- and monobromobenzene appear to be completely absorbed, but hexachlorobenzene was "poorly" absorbed by rabbits. Fewer data were located for the halogenated

naphthalenes. Rapid absorption of ~62% of an oral dose was measured for 1,2-dichloronaphthalene in rats (U.S. EPA, 1980b). Gastrointestinal absorption of ~89% in rats was observed for a mixture of hexabromonaphthalenes (Birnbaum et al., 1983).

Data could not be located comparing the gastrointestinal absorption of chlorinated with brominated dibenzo-p-dioxins or dibenzofurans. Data with 2,3,7,8-TCDD demonstrate the impact of vehicle on efficiency of absorption, as absorption efficiencies of 50-60% and 70-86% were measured in rats exposed in diet or oily vehicle, respectively. Adsorption on soil or activated carbon markedly reduced or prevented gastrointestinal absorption (U.S. EPA, 1985a).

For those halogenated homologues for which data are available, it appears that gastrointestinal absorption occurs rapidly and to a similar extent, regardless of whether the halogen is bromine or chlorine.

4.2. DISTRIBUTION

Following absorption, chlorinated and brominated biphenyls (Becker and Gamble, 1982; Matthews et al., 1984; Maliwal and Guthrie, 1982) and presumably other halogenated aromatic hydrocarbons (Birnbaum, 1985) form a loose association with the lipoprotein fraction of the blood. The proportion of a dose of PCBs associated with lipoprotein increases with increasing halogenation (Matthews et al., 1984). Approximately 30% of an *in vitro* dose of unsubstituted biphenyl, 40% for 4-chlorobiphenyl, 50% for 4,4'-PCB and 60% for 2,4,5,2',5'-PCB was loosely bound to lipoprotein. 2,4,5,2',4',5'-PCB and PBB were both 80% associated with lipoprotein, suggesting that chlorinated and brominated compounds behave similarly in this regard (Matthews et al., 1984).

Distribution of these compounds and their metabolites appears to be biphasic, with an initial rapid distribution to highly vascular tissues and muscle that results in a lowering of blood content to the equivalent of ≤10% of the administered dose within 15 minutes of an intravenous administration (Matthews and Anderson, 1975a,b; Matthews et al., 1974). This is followed by redistribution to liver or fat as terminal depots of storage (Birnbaum, 1985). For the PCBs, for which most data are available, distribution patterns are qualitatively similar in rats and mice treated by intravenous, oral or intraperitoneal administration (Matthews and Anderson, 1975a,b; Matthews et al., 1974; Morales et al., 1979; Micelli and Marks, 1981). The proportion of the tissue burden of PCBs that exist as metabolites decreases with increasing chlorination and is always least in adipose tissue (Matthews and Anderson, 1975a,b; Matthews et al., 1974). For 2,4,5,2',4',5'-PCB and its homologous PBB congener, <1% of the burden in fat was associated with metabolites (Matthews and Anderson, 1975a; Matthews et al., 1974, 1977). The peak amount of these hexahalogenated congeners in fat (expressed in proportion of administered dose) was not determined, because retention in fat continued as the animals aged and fat became a larger proportion of total body mass. Experiments with a mixture of PBBs in rats (Domino et al., 1980) suggest that these compounds undergo biphasic distribution similar to that of the PCBs. For both these classes of compounds, the rate of metabolism is the major factor that influences the kinetics of retention in adipose tissue (Birnbaum, 1985).

Experiments with PCBs in rats (Lucier et al., 1977) and mice (Vodicnik, 1986; Vodicnik and Lech, 1980) and with PCBs and PBBs in mink (Bleavins et al., 1981) indicated that the placenta is a partial barrier to the transfer of these compounds to the fetus. In humans exposed to PBBs, levels in

maternal serum exceeded those in fetal (cord) blood by a factor of 6-10 (Eyster et al., 1983). PCBs and PBBs appear to behave similarly in this regard.

The distribution of the halogenated benzenes, naphthalene, dibenzo-p-dioxins and dibenzofurans appear to be similar to that of the PCBs and PBBs, except that highly chlorinated naphthalene (Birnbaum, 1983) 2,3,7,8-TCDD (U.S. EPA, 1985a) and 2,3,7,8-TCDF (Birnbaum, 1985) may redistribute preferentially to liver rather than to fat. Data comparing chlorinated and brominated members of these classes could not be located.

4.3. METABOLISM

In most cases it appears that metabolism is a prerequisite for efficient excretion (Birnbaum, 1985). The primary metabolic step is oxidation, resulting in the addition of a hydroxyl group at one or more positions on the aromatic ring(s). Oxidation by arene oxide formation has been postulated as the predominant mechanism of hydroxylation for all the halogenated aromatic hydrocarbons (Kohli et al., 1976; Kohli and Safe, 1976; Ogino, 1984a,b; Ruzo et al., 1976b; Kato et al., 1980; Matthews and Anderson, 1975a). Halogen shifts (Ruzo et al., 1976a,b) and dehalogenation (Ogino, 1984a,b) were cited as evidence for arene oxide formation.

Qualitatively, the metabolism of the chlorinated and brominated homologues of benzene, naphthalene and biphenyl appears to be similar. Experiments with the halogenated benzenes (U.S. EPA, 1980b,c; Ruzo et al., 1976a; Ogino, 1984a) indicate that the nature of the halide influences the nature of the products that result from the breakdown (isomerization) of the arene oxide intermediate. The relative quantities of oxidation products, therefore, may differ between chlorinated and brominated homologues.

Tetra- and hexachlorinated and brominated biphenyl homologues appear to be metabolized at virtually identical rates (Millis et al., 1985), but marked differences in metabolic rate in an *in vitro* system with rat hepatic microsomes was noted with four 4-monohalogenated biphenyls (Parkinson and Safe, 1982). These investigators also noted marked differences in the extent to which pretreatment with PB or MC accelerated the rate of metabolism of the four 4-monohalogenated biphenyls.

Generally, for the halogenated benzenes, naphthalenes and biphenyls, the rate of metabolism decreases with increasing halogenation (U.S. EPA, 1980b,c; Ruzo et al., 1976a; Ogino, 1984a; Moore et al., 1980; Safe, 1980; Birnbaum, 1985). For the halogenated biphenyls, metabolism is enhanced by the presence of adjacent unsubstituted carbon atoms and, in particular, by unsubstituted para positions on at least one ring (Safe, 1980; Moore et al., 1980).

Marked differences were noted in the rate of metabolism of 2,3,7,8-TCDD (U.S. EPA, 1985b) and 2,3,7,8-TCDF (U.S. EPA, 1984c) among species. The presence of vicinal unsubstituted carbon atoms may also facilitate metabolism of these halogenated aromatic compounds. Data comparing the metabolism of chlorinated and brominated dibenzo-p-dioxins and dibenzofurans could not be located.

4.4. EXCRETION

Although few data comparing the excretion of the brominated and chlorinated aromatic hydrocarbons were located, generalizations have been postulated from data obtained with the chlorinated compounds (Birnbaum, 1985). The rate of excretion depends predominantly on the rate of metabolism, as most of these compounds must be metabolized before efficient excretion can occur (Birnbaum, 1985). Excretion is predominantly urinary or fecal

(biliary), with the molecular weight of the metabolite determining the principal route of excretion (Birnbaum, 1985; Ogino, 1984a; Chu et al., 1977; Matthews and Anderson, 1975a; Matthews et al., 1977). For some compounds, intestinal absorption and urinary excretion of biliary metabolites may obscure the importance of biliary excretion. For those few compounds that are fairly volatile (monochloro- and monobromobenzene), expiration of unchanged compound also occurs (U.S. EPA, 1977, 1980c). Data comparing the excretion of homologous chlorinated and brominated compounds were located only for monohalobenzene and 2,4,5,2',4',5'-polyhalogenated biphenyls. For the monohalogenated benzenes, recovery of orally administered compound was virtually complete from rabbits within 2 days (U.S. EPA, 1977). Excretion was by the urine except for 27% of the dose of chlorobenzene and 6% of the dose of bromobenzene recovered as parent compound from expired air. Expiration of these unchanged compounds is probably due to their volatility as reflected by their vapor pressures (15.5 mm Hg for chlorobenzene and 5.7 mm Hg for bromobenzene).

When ^{14}C-2,4,5,2',4',5'-PCB or the homologous PBB were administered intravenously to rats, <1% of the dose of radioactivity was recovered in the urine (Kato et al., 1980; Birnbaum, 1983; Matthews et al., 1977; Tuey and Matthews, 1980). Fecal excretion accounted for <7% of the dose of radioactivity associated with either compound. Most of the radioactivity was sequestered in the body fat. These studies with homologous halogenated benzenes and biphenyls indicate that the modes of excretion of the chlorinated and brominated compounds are similar.

Experiments in mice (Vodicnik, 1986; Vodicnik and Lech, 1980), rats (Lucier et al., 1977), mink (Bleavins et al., 1981) and lactating dairy cattle (Willett and Durst, 1978) indicate that lactation is an important

route of excretion for the halogenated biphenyls, especially those that are resistant to metabolism and tend to bioaccumulate in fat. The chlorinated compounds and their brominated homologues appear to behave similarly (Lucier et al., 1977).

Data comparing brominated and chlorinated dibenzo-p-dioxins and dibenzofurans could not be located. Experiments with 2,3,7,8-TCDD and TCDF (U.S. EPA, 1984c, 1985b) indicate marked species differences in routes of excretion and elimination half-lives.

4.5. SUMMARY

Qualitatively, the chlorinated and brominated aromatic hydrocarbons appear to have similar pharmacokinetic behavior. For those halogenated homologues for which data are available, it appears that gastrointestinal absorption occurs rapidly and to a similar extent regardless of whether the halogen is bromine or chlorine (Albro and Fishbein, 1972; Matthews and Anderson, 1975a; Morales et al., 1979; Matthews et al., 1977; Iuey and Matthews, 1980).

Following absorption, the halogenated hydrocarbons form a loose association with the lipoproteins of the blood (Matthews et al., 1984; Becker and Gamble, 1982; Maliwal and Guthrie, 1982; Birnbaum, 1985), rapidly distribute from the bloodstream to highly vascular tissues and muscle (Matthews and Anderson, 1975a,b; Matthews et al., 1974) and then redistribute to fat or tissue as terminal depots of storage (Birnbaum, 1985). The placenta appears to be a partial barrier to the transfer of these compounds to the fetuses of animals (Lucier et al., 1977; Vodicnik, 1986; Vodicnik and Lech, 1980; Bleavins et al., 1981) and humans (Eyster et al., 1983).

Metabolism appears to be a prerequisite for the efficient excretion of most of the halogenated aromatic hydrocarbons (Birnbaum, 1985). The primary step is oxidation, apparently through an arene oxide intermediate (Kohli et al., 1976; Ogino, 1984a,b; Ruzo et al., 1976a,b; Kato et al., 1980; Matthews and Anderson, 1975a). There appear to be few major differences in metabolism between homologous chlorinated and brominated compounds, although the relative proportions of oxidation products resulting from the isomerizations of the arene oxide intermediates may differ (Ruzo et al., 1976a; Ogino, 1984a). Generally, for the halogenated benzenes, naphthalenes and biphenyls, the rate of metabolism decreases with increasing halogenation (Ruzo et al., 1976a; Ogino, 1984a; Moore et al., 1980; Safe, 1980) although for the biphenyls metabolism is enhanced by the presence of adjacent unsubstituted carbon atoms and, in particular, by unsubstituted para positions on at least one ring (Safe, 1980; Moore et al., 1980).

The rates of excretion of the halogenated aromatic hydrocarbons depend primarily on their rates of metabolism (Birnbaum, 1985). Comparative data with chlorinated and brominated monohalobenzene (U.S. EPA, 1977) and homologous hexahalogenated PCB and PBB (Kato et al., 1980; Birnbaum, 1983; Matthews et al., 1977; Tuey and Matthews, 1980) suggest that the routes and rates of elimination of the chlorinated compounds are similar to the brominated compounds. Lactation is an important route of excretion for those PCBs and PBBs that resist metabolism and tend to accumulate in body fat.

5. EFFECTS

5.1. TOXICITY

Moore et al. (1979) was the only study in which the toxicities of chlorinated and brominated dibenzofurans were compared directly. In this study, acute toxicity of 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 2,3,7,8-tetrabromodibenzofuran (TBDF) was tested in guinea pigs. Groups of six male guinea pigs received single oral doses of 3.3, 16.3, 32.7 or 49.0 nmol/kg TCDF or 1.0, 3.3, 9.8 or 32.7 nmol/kg TBDF. Controls consisted of nine guinea pigs. Animals were observed for 30 days after dosing. Among the animals that eventually died, signs of toxicity were similar for both compounds. These included progressive weight loss, with body weights at death being 50% of those at time of dosing. Other signs of toxicity were rough coat, listlessness and dehydration. All animals receiving 32.7 or 49.0 nmol/kg TCDF died 9-20 days after dosing; mean times to death were 11.8 days at 49.0 nmol/kg and 14.6 days at 32.7 nmol/kg. No deaths occurred at 16.3 or 3.3 nmol/kg, although decreased body weight gain occurred in these groups. All animals receiving 32.7 nmol/kg TBDF died, with a mean time to death of 11.7 days. One guinea pig that received 9.8 nmol/kg TBDF died 26 days after dosing, and the other five that survived showed decreased body weight gain. No deaths or body weight effects occurred in the 1.0 or 3.3 nmol/kg TBDF groups. The quantitative effects of these compounds are therefore quite similar. The pattern of histopathological lesions in animals that died was similar for both compounds. These lesions included epithelial hyperplasia in the renal pelvis, ureter and urinary bladder, and loss of lymphoid cells in the thymic cortex. Other effects included reduced size of thymus, reduced muscle mass and lack of body fat. The only histopathological effect found in surviving guinea pigs was mild thymus lymphoid hypo-

plasia. These effects are similar to those caused by halogenated dibenzo-dioxins and other halogenated aromatic compounds (Moore et al., 1979).

Yang et al. (1983) was the only study in which the effects of chlorinated and brominated dioxins were compared directly. Groups of 5-6 male Sprague-Dawley rats were given single oral doses of 25 µg/kg of 2,3,7,8-TCDD, 2,3,7-tribromodibenzo-p-dioxin (TBDD) or other chlorinated dibenzo-p-dioxins. Both 2,3,7,8-TCDD and 2,3,7-TBDD increased the plasma concentration of ouabain and decreased its excretion into the bile, decreased bile flow and increased liver weight. These effects were more severe in rats treated with 2,3,7,8-TCDD than in rats treated with 2,3,7-TBDD. Body weight was decreased by 2,3,7,8-TCDD but not 2,3,7-TBDD. Because these compounds do not have the same degree of halogenation, differences in effects cannot be attributed solely to the effect of bromine vs. chlorine substitution.

Most of the other available data comparing the toxicity of brominated and chlorinated aromatic compounds pertain to PCBs and PBBs. Much of this information comes from studies in which commercial mixtures of isomers were used and therefore is useful only for qualitative comparisons. PCBs and PBBs cause a similar pattern of toxic effects, including increased relative liver weight (Babish and Stoewsand, 1977; Garthoff et al., 1977; Waritz et al., 1977), liver lesions (Kimbrough, 1980; McKinney et al., 1976), reduced body weight gain (Akoso et al., 1982a; Garthoff et al., 1977; Goldstein et al., 1977; NTP, 1983; Render et al., 1982), reduced thymus size (Akoso et al., 1982a; Dannan et al., 1982; McKinney et al., 1976) and thyroid effects (Collins et al., 1977; Kasza et al., 1978; NTP, 1983). PCBs and PBBs also cause effects on vitamin A metabolism (Cullum and Zile, 1985; McCormack et al., 1982a; Innami et al., 1976), liver membrane transport processes (Eaton

and Klaassen, 1979; Manis and Kim 1979, 1980; Reich et al., 1981), liver lipids (Bernert and Groce, 1984; McCormack et al., 1982b) and increased urinary porphyrins (McCormack et al., 1982a; NTP, 1983).

Pure PCB or PBB isomers were used in some studies and this provides a basis for a more quantitative comparison of toxicity. Akoso et al. (1982a,b) administered three hexabromobiphenyl (HBB) isomers to rats in the diet (0, 1, 10 and 100 ppm) for 30 days. The isomers were 2,2',4,4',5,5'-HBB, 2,3',4,4',5,5'-HBB and 3,3',4,4',5,5'-HBB (only 0, 1 and 10 ppm for this compound). All three compounds caused liver enlargement, vacuolization and enlargement of hepatocytes (Akoso et al., 1982a) and thyroid lesions (Akoso et al., 1982b). The 3,3'-isomer had the most severe effects on liver and thyroid and the 2,2'-isomer the least severe effects. The 3,3'-isomer also caused thymic and splenic atrophy, reduced feed efficiency and weight gain (high dose only), and changes in vitamin A metabolism. The authors concluded that the 3,3'-isomer was the most toxic, 2,2' the least toxic and 2,3' intermediate in toxicity (Akoso et al., 1982a,b).

Render et al. (1982) conducted a similar study comparing the toxicity of 2,2',4,4',5,5'-HBB and 3,3',4,4',5,5'-HBB administered in the diet (0, 0.1, 1, 10 or 100 ppm) of rats for 9 days. Once again the 3,3'-isomer was more toxic, causing decreased food intake and body weight gain, decreased thymus and spleen weights and severe lymphocytic depletion in the thymic at 10 and 100 ppm. These levels are quantitatively similar to the 3,3',4,4',5,5'-HBB results of Akoso et al. (1982a,b). Both compounds caused increased relative liver weights and enlargement and vacuolization of hepatocytes at 10 and 100 ppm. The 3,3',4,4',5,5'-HBB isomer caused more severe liver lesions than 2,2',4,4',5,5'-HBB.

Biocca et al. (1981) administered various hexachlorobiphenyl (HCB) isomers to male mice (five per dose level) in the diet at concentrations of 0, 10, 30, 100 and 300 ppm for 28 days. In addition, concentrations of 0.3, 1 and 3 ppm 3,3',4,4',5,5'-HCB were used. As was the case with HBBs (Akoso et al., 1982a,b; Render et al., 1982), the 3,3',4,4',5,5'-isomer was the most toxic, causing dose-related mortality at 30, 100 and 300 ppm. It also caused reduced body weight gain at concentrations $\geq$3 ppm. Liver enlargement and dose-related histological effects in the liver occurred at all dosages. Depletion of lymphocytes in the spleen and moderate atrophy of the thymus occurred at $\geq$3 ppm. These results are quantitatively and qualitatively similar to those obtained for 3,3',4,4',5,5'-HBB by Akoso et al. (1982a) and by Render et al. (1982). Mortality and body weight effects occurred in treated mice only at 300 ppm 2,2',4,4',5,5'-HCB and 2,2',4,4',6,6'-HCB. The next most toxic isomer was 2,2',4,4',6,6'-HCB, which caused marked fatty metamorphosis of the liver and atrophy of the thymus and spleen at 300 ppm, and moderate histological liver effects at 100 ppm. Slight to moderate histological effects occurred at 100 and 300 ppm 2,2',4,4',5,5'-HCB and 2,2',3,3',6,6'-HCB. Slight thymus atrophy also occurred at 300 ppm 2,2',4,4',5,5'-HCB. The authors concluded that the order of decreasing overall toxicity was 3,3',4,4',5,5'-HCB >> 2,2',4,4',6,6'-HCB > 2,2',4,4',5,5'-HCB > 2,2',3,3',6,6'-HCB.

McKinney et al. (1976) reported similar results for HCBs administered to chicks in their diet (400 ppm). The 3,3',4,4',5,5'-HCB isomer was most toxic in terms of mortality, producing edema and thymic involution. It did not cause "appreciable pathological changes in the liver," while 2,2',4,4',6,6'-HCB caused "marked" changes and 2,2',3,3',4,4'-HBB "moderate" changes. In terms of decreased growth, increased liver weight, liver pathology and mortality, the authors ranked the five HCB isomers in order of

decreasing toxicity as follows: 3,3',4,4',5,5'-HCB > 2,2',4,4',6,6'-HCB ≥ 2,2',3,3',4,4'-HCB = 2,2',4,4',5,5'-HCB > 2,2',3,3',6,6'-HCB. Once again, the 3,3',4,4',5,5'-isomer was the most toxic, as was the case with HBBs in the previously described studies (Akoso et al., 1982a,b; Render et al., 1982).

Goldstein et al. (1977) reported similar results for HCBs administered to rats by intraperitoneal injection. The 3,3',4,4',5,5'-isomer was more toxic than the 2,2',4,4',5,5'-isomer, as measured by weight loss.

Qualitatively, PCBs and PBBs cause a similar pattern of toxic effects. The structure-toxicity relationships also appear to be similar for both sets of compounds. Halogenation of PBBs and PCBs in the ortho positions (2,6,2',6') reduces their toxicity (Dannan et al., 1982; Goldstein et al., 1977). The limited quantitative data for pure PCB and PBB isomers also suggest that the compounds have similar toxic potencies.

Other investigators have made comparisons of chlorinated and brominated benzene compounds. Carlson (1977, 1978) studied porphyrinogenic effects of chlorinated and brominated benzenes. Carlson (1977) found that 1,4-dichlorobenzene, 1,2,4-trichlorobenzene and hexachlorobenzene (0, 50, 100 or 200 mg/kg orally for 30-120 days) all caused an increase in relative liver weights in female rats, but only hexachlorobenzene caused an increase in liver porphyrin levels and urinary excretion of porphyrins. In a study with the same experimental design, Carlson (1978) determined that 1,4-dibromobenzene, 1,2,4-tribromobenzene and hexabromobenzene caused increases in relative liver weights, but none caused porphyria. The difference between hexachlorobenzene, which was highly porphyrinogenic, and hexabromobenzene, which was a poor inducer of porphyria, was particularly striking. Mendoza et al. (1977, 1979) also compared the effects of hexachlorobenzene and hexabromobenzene. Mendoza et al. (1977) fed male rats diets containing

10-160 ppm hexabromobenzene for 12 weeks. No effects on body weight, organ weights or hematological parameters occurred. There was a tendency toward increased liver porphyrin concentration with increasing dosage, but this was not statistically significant. Mendoza et al. (1979) fed female rats diets containing 0 or 80 ppm hexabromobenzene or hexachlorobenzene from 2 weeks before mating until 35-66 days after weaning (101 days total). Neither compound affected gestation, neonatal survival or maternal organ weight and body weights. Hexabromobenzene caused a significantly higher liver porphyrin level than occurred in the hexachlorobenzene-treated group or controls. Mendoza et al. (1979) concluded that hexabromobenzene was more porphyrinogenic than hexachlorobenzene in female rats, a finding contradictory to the results of Carlson (1977, 1978). This could have been caused by the fact that different rat strains (Sprague-Dawley and Wistar) were used by the two investigators. Both authors agreed that female rats were more sensitive to halogenated benzene-induced porphyria than males.

5.2. CARCINOGENICITY

Data concerning the carcinogenicity of brominated dibenzo-p-dioxins and brominated dibenzofurans are not available. However, comparative information concerning the carcinogenicity of brominated vs. chlorinated aromatic compounds pertaining to PBBs and PCBs is available. Both sets of compounds act primarily on the liver, causing hepatocellular carcinomas (Groce and Kimbrough, 1984; NTP, 1983; Sleight, 1985). The available evidence suggests that both PCBs and PBBs act as promoters rather than complete carcinogens (Jensen et al., 1982; Sleight, 1985; Tsushimoto et al., 1982b). Most of the available information is only useful for qualitative comparisons because it pertains to commercial PCB and PBB mixtures rather than pure isomers.

Sleight (1985), however, did provide information regarding the promoting activity of specific PBB isomers in rats and mice. He found that toxicity and carcinogenicity were not necessarily related. Some of the more toxic PBBs (for example, 3,3',4,4',5,5'-HBB) were promoters only at hepatotoxic doses, indicating that carcinogenicity was a secondary effect. Other PBBs that were relatively nontoxic (for example, 2,2',4,4',5,5'-HBB) acted as promoters at nonhepatotoxic doses. Sleight (1985) also demonstrated a synergistic effect on tumor promotion by combining a nontoxic, nonpromoting dose of 3,3',4,4',5,5'-HBB with a promoting dose of 2,2',4,4',5,5'-HBB. This may explain why certain commercial PBB mixtures have greater promoting activity than individual congeners.

Tsushimoto et al. (1982b) conducted in vitro assays with various PBB congeners comparing their cytotoxicity and ability to inhibit metabolic cooperation in Chinese hamster cells. The property of inhibiting metabolic cooperation is associated with known tumor promoters. These results agreed with those of Sleight (1985) in that the most cytotoxic congeners (for example, 3,3',4,4',5,5'-HBB) did not inhibit metabolic cooperation, while less cytotoxic congeners such as 2,2',4,4',5,5'-HBB strongly inhibited metabolic cooperation. Tsushimoto et al. (1982b) concluded that the ability to inhibit metabolic cooperation was directly related (and cytotoxicity inversely related) to the degree of bromination in the ortho position.

Tsushimoto et al. (1983) conducted similar experiments with PCBs and PBBs and their cytotoxicity and ability to inhibit intracellular communication (metabolic cooperation) in Chinese hamster cells. They found that 3,3',4,4',5,5'-HCB was much more cytotoxic than 2,2',4,4',5,5'-HCB, while the latter inhibited intracellular communication to a much greater extent.

This is analogous to HBBs (Isushimoto et al., 1982b). Isushimoto et al. (1983) also compared analogous HBB and HCB congeners (2,2',4,4',5,5'-HCB and 2,2',4,4',5,5'-HBB). Both compounds inhibited intracellular communication, and the HCB compound was slightly more cytotoxic.

In vitro assays with pure isomers indicated qualitative similarities in the tumor-promoting activities of PBB and PCB analogs (Sleight, 1985; Tsushimoto et al., 1982b, 1983).

Although brominated dibenzo-p-dioxins and dibenzofurans have not been tested for carcinogenicity, information concerning the carcinogenicity of closely related chlorinated dibenzo-p-dioxins is available and may be useful for qualitative comparisons.

U.S. DHHS (1980a) reported an NCI bioassay of 2,3,7,8-TCDD in which 30 male and female Swiss-Webster mice were dermally treated with an acetone suspension of TCDD for 3 days/week for 104 weeks. Similar groups were pretreated with one application of 50 µg dimethylbenzoanthracene (DMBA) in 0.1 mL acetone 1 week before TCDD administration began. Female mice received 0.005 µg TCDD per application and male mice received 0.001 µg TCDD. It was concluded that under the conditions of this bioassay, TCDD applied to the skin was carcinogenic for female Swiss-Webster mice inducing increased incidences of fibrosarcomas in the integumentary system.

Kociba et al. (1978) reported a more extensive carcinogenicity study on TCDD. Groups of 100 Sprague-Dawley rats (50/sex/group) were maintained for up to 2 years on diets containing 0.001, 0.01 and 0.1 µg TCDD/kg/day. Controls consisted of 86 males and 85 females. Extensive histopathologic and clinical chemistry evaluations were conducted. Statistically significant neoplastic lesions were found in males (adrenal cortical adenomas and

squamous carcinomas of the tongue), females (hepatocellular carcinomas and neoplastic nodules and carcinomas of the lung) and in males and females (squamous cell carcinomas of the palate and nasal turbinae).

A bioassay of 2,3,7,8-TCDD was conducted in Osborne-Mendel rats and B6C3F1 mice for 104 weeks (U.S. DHHS, 1980b). Fifty rats and mice of each sex were administered by gavage TCDD suspended in a 9:1 octane-corn oil vehicle for 2 days/week at doses of 0.01, 0.05 or 0.5 μg/kg/day for rats and male mice and 0.04, 0.2 or 2.0 μg/kg/day for female mice. Under the conditions of this bioassay, TCDD was carcinogenic for Osborne-Mendel rats, inducing significant dose-related increased incidences of follicular-cell thyroid tumors in males and liver tumors in females. TCDD was also carcinogenic for B6C3F1 mice inducing significant dose-related incidences of liver tumors in males and females and thyroid tumors and fibrosarcomas of subcutaneous tissue in females (U.S. DHHS, 1980b). 2,3,7,8-TCDD has also been shown to be a potent promoter of hepatocarcinogenesis (Pitot et al., 1980).

Hexachlorodibenzo-p-dioxin (HCDD) has also been tested for carcinogenicity in rats and mice treated by gavage (U.S. DHHS, 1980c) and by dermal application to mice. In these studies, a 1:2 mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD was tested. In the oral study, animals received HCDD at doses of 0, 1.25, 2.5 or 5.0 μg/kg/week except for females, which received 0, 2.5, 5.0 or 10.0 μg/kg/week. In both species and both sexes, only tumors of the liver occurred at significantly greater incidences than in the controls. In male rats and female and male mice the incidence of liver tumors was significant only at the high dose while in female rats the incidence was greater at both the medium and high dose levels. In the study in mouse skin (U.S. DHHS, 1980d), there were no treatment-related tumors in either the carcinogenicity or tumor promotor assay.

NCI (1979) reported a bioassay of 2,7-dichlorodibenzo-p-dioxin (DCDD) in Osborne-Mendel rats and B6C3F1 mice. Groups of 35 rats or 50 mice of each sex were administered 5000 or 10,000 ppm DCDD in their diet for 110 and 90 weeks, respectively. It was concluded that under the conditions of this assay DCDD was not carcinogenic for Osborne-Mendel rats of either sex or for female B6C3F1 mice and only suggestive of a carcinogenic effect in male mice.

U.S. EPA (1984c) concluded that because of the induction of hepatocellular carcinomas in two strains of female rats and both sexes of one mouse strain, along with the induction of fibrosarcomas, lung, tongue and thyroid tumors in both rats and mice, that TCDD was carcinogenic in animals and probably carcinogenic to humans. The evidence for human carcinogenicity based on epidemiologic studies is only suggestive because TCDD exposure is almost always confounded by exposure to other chemicals such as chlorophenols or phenoxy acids. It was also concluded that HCDD was a weak hepatocellular carcinogen in female rats and mice.

Based on the proposed Carcinogen Assessment Guideline (U.S. EPA, 1986), the brominated dioxins and dibenzofurans would be placed in category D. This would indicate that currently no carcinogenic data are available. However, considering the structure-activity analysis of the brominated dibenzo-p-dioxins and dibenzofurans with the closely related chlorinated dibenzo-p-dioxins, these compounds may have carcinogenic potential.

5.3. REPRODUCTIVE EFFECTS

Most of the data concerning reproductive effects of brominated and chlorinated aromatic compounds applies to PCBs and PBBs and is generally useful only for qualitative comparisons. Allen et al. (1979) found that PCBs, PBBs and 2,3,7,8-TCDD disrupted the menstrual cycle of rhesus monkeys.

This effect may be caused by hormone imbalances since PCBs and PBBs induce liver enzymes (MFOs) that metabolize steroid sex hormones (Arneric et al., 1980). Allen et al. (1979) also reported that infant birth weights were lower in offspring of PCB- and PBB-treated monkeys.

Lucier et al. (1977) compared effects of chlorinated and brominated biphenyls on the offspring of CD-1 mice treated orally on days 10-16 of gestation. Dosages were 0.3-32.0 mg/kg/day of 3,3',4,4'-tetrachlorobiphenyl ("4-CB"), 2,2',4,4',5,5'-hexachlorobiphenyl("6-CB") and 2,2',4,4',5,5'-hexabromobiphenyl ("6-BB"). The high dose 4-CB treated mice experienced decreased litter sizes and survival rates of offspring, an increased incidence of soft tissue anomalies and behavioral changes. No evidence of fetotoxicity or teratogenicity was seen in mice treated with 6-CB or 6-BB.

Welsch and Morgan (1985) fed pregnant B6C3F1 mice diets containing 0, 100, 300, 500, 750 or 1000 ppm 2,2',4,4',5,5'-HBB on days 6-15 of gestation. Embryotoxicity and maternal toxicity were evident at 300 ppm and above. Effects included decreased pregnancy rates, decreased maternal weight gain, and cleft palate and cystic brain lesions in offspring. Some maternal mortality occurred at 750 and 1000 ppm. Minor abnormalities in brain development occurred, but the authors attributed this to delayed development rather than a teratogenic effect. The authors concluded that this compound only affected embryonic development at doses that were toxic to the dams.

Aulerich and Ringer (1977, 1979) compared the toxicity and reproductive effects of commercial PCB (Aroclor 1254) and PBB (Firemaster FF-1) mixtures on mink. The PBB mixture was more toxic, with an LD_{50} of 3.95 ppm in the diet for 313 days, compared with 6.65 ppm Aroclor 1254 in the diet for 280-297 days. The PBB mixture impaired reproduction when administered at 1-25 ppm in the diet for 9 months. Effects included decreased litter sizes,

body weight of offspring and litter survival. The PCB mixture caused more severe reproductive effects, resulting in nearly complete reproductive failure (embryotoxicity) when fed at a dietary concentration of 2 ppm for 7 months before breeding (Aulerich and Ringer, 1977). Aroclor 1254 and Firemaster FF-1 are commercial mixtures of PCB and PBB isomers and, as such, they probably differ in isomeric composition, degree of halogenation and level of impurities, in addition to the chlorine vs. bromine difference (Biocca et al., 1981). Therefore, it is difficult to attribute observed differences in reproductive effects solely to the different effects of bromine and chlorine substitution.

Analogous hexachloro- and hexabromobiphenyl compounds (2,2',4,4',5,5') did not cause any fetotoxic or teratogenic effects in mice receiving oral doses of 0.3-32.0 mg/kg/day on days 10-16 of gestation (Lucier et al., 1977). The only other studies in which PCBs and PBBs were compared directly were those of Aulerich and Ringer (1977, 1979), who fed diets containing commercial PCB and PBB mixtures to mink. The PCB mixture caused more severe reproductive effects, but this result is of questionable significance because the mixtures differed in isomeric composition, degree of halogenation and level of impurities, in addition to the differences in chlorine and bromine substitution.

6. STRUCTURE-ACTIVITY RELATIONSHIPS

6.1. CHLORINATED AROMATICS -- GENERAL CONSIDERATIONS

Structure-activity relationships for chlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans have been extensively studied and will be briefly reviewed before a discussion of the more limited data on the brominated congeners. Recent publications on structure-activity relationships of chlorinated aromatics include those by Bandiera et al. (1983, 1984), Leece et al. (1985), McKinney et al. (1984, 1985a,b), Poland et al. (1983), Safe (1986) and Safe et al. (1985a,b). The most common measures of biological activity of PCDDs, PCDFs, PCBs and related compounds are binding to the Ah receptor protein and the induction of AHH and EROD. Receptor binding is normally measured by the competitive displacement of [^{3}H]-TCDD from the receptor protein by the congener and is expressed as the concentration of the congener required to reduce the specific binding of [^{3}H]-TCDD by one-half (EC_{50}). The induction of AHH and EROD also are expressed as EC_{50}s but refer to the concentration of the congener required to produce half-maximal induction of the enzyme.

The relationship of receptor binding affinities of PCDD and PCDF congeners to the position of chlorine substituents has been summarized by Safe (1986) (Figure 8-1). For the chlorinated dioxins, chlorine substituents in the lateral (-2,3,7,8) positions enhance binding, while substituents in the nonlateral (-1,4,6,9) positions diminish binding. For significant receptor binding, at least three of the four lateral positions must have chlorine substituents. The decrease in binding affinity with increased chlorine substitution in the nonlateral positions may be related to steric crowding, resulting in a decrease in PCDD coplanarity or other factors such as decreases in the electron density of the aromatic ring or increases in

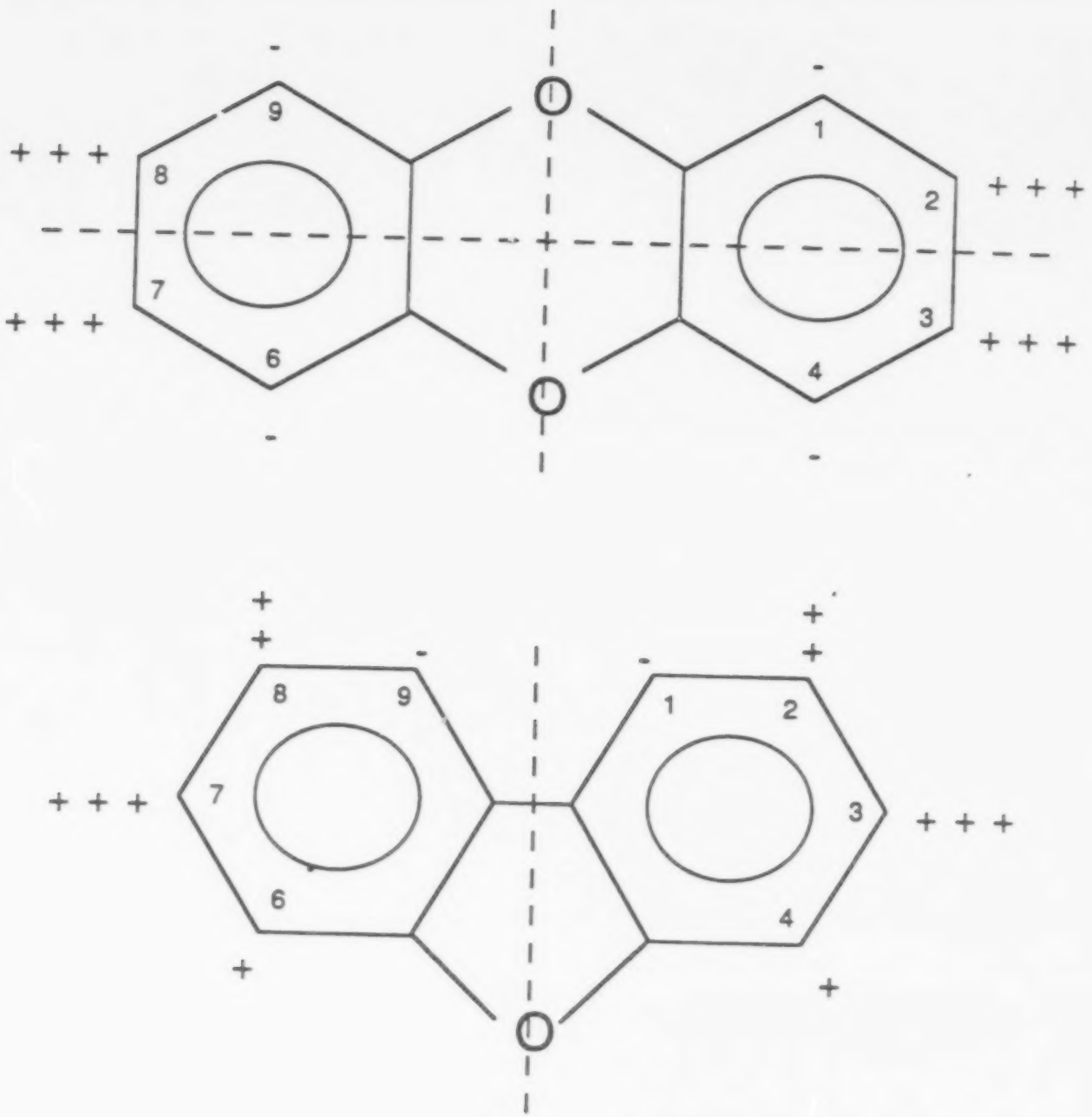


FIGURE 6-1

Relationship of Receptor Binding Affinities of PCDD and PCDF Congeners to the Position of Chlorine Sutstituents

Source: Safe, 1986

molecular size, volume or lipophilicity. For the chlorinated dibenzofurans, receptor binding is enhanced by substitution at the C-3 and C-7 positions, substantially enhanced by substitution at the C-2 and C-8 positions and less markedly enhanced by substitution at the C-4 and C-6 positions. Substitution at the C-1 and C-9 positions diminishes activity. For both the PCDDs and PCDFs, quantitative structure-activity analyses have indicated that receptor binding is most clearly correlated with lipophilicity. While AHH and EROD induction potency can be related to receptor binding, the relationship is not linear. Quantitative structure-activity relationships have demonstrated that terms for both lipophilicity and substituent width are required to account for the effect of structure on the induction of these enzymes by PCDDs and PCDFs (Safe, 1986).

PCBs, like PCDDs and PCDFs, bind with the receptor and induce AHH and EROD. In general, PCBs substituted at the para and meta positions are more active than those substituted at the ortho position. The decrease in receptor binding and enzyme induction with ortho substitution may be related to the decrease in coplanarity (Safe et al., 1985a). Poland and Knutson (1982) suggested that receptor binding and biological activity of PCDDs, PCDFs, PCBs and related chlorinated aromatics may be related to a planar or coplanar ring configuration and the ability to occupy a 3x10 Å binding area.

6.2. HALOGENATED DIOXINS

Although the brominated dioxins, dibenzofurans and biphenyls have not been as extensively studied as their chlorinated congeners, the results of several studies suggest that the substitution of chlorine by bromine is likely to enhance or at least not markedly diminish the biological activity of these compounds in terms of receptor binding and enzyme induction. This

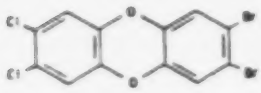
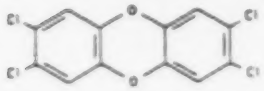
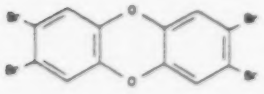
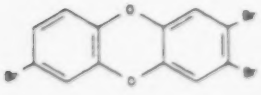
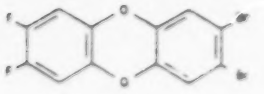
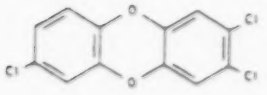
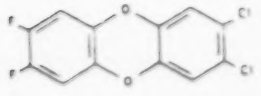
was first suggested in studies by Kende et al. (1974) and Poland et al. (1976), who assayed a series of brominated, chlorinated and fluorinated dioxins for AHH induction and receptor binding. As summarized in Table 6-1, 2,3,7,8-tetrabromodibenzo-p-dioxin is as potent as the 2,3,7,8-chlorinated isomer, as measured by AHH induction. Substitution of the lateral chlorines of the tetrachlorinated isomer by two bromines slightly enhances AHH induction. A much more pronounced difference is apparent in AHH induction between the 2,3,7-tribromo- and 2,3,7-trichlorodioxins, with the brominated compound being more potent than the chlorinated compound by a factor of 30 and 700 in the studies by Kende et al. (1974) and Poland et al. (1976), respectively. A similar pattern is seen when comparing the dibromodifluoro-dioxin to the dichlorodifluorodioxin, with the brominated compound being ~20 times more active than the chlorinated compound in inducing AHH. Comparative receptor binding data are presented only for the 2,3,7-tribromo- and trichlorodioxins; the brominated compound has an ~3-fold greater affinity for the receptor than the chlorinated compound.

Earlier work by Poland and Glover (1973) also suggested that 2,3,7-tribromodibenzo-p-dioxin was more effective than the 2,3,7-trichlorodioxin in the induction of AHH activity and ALA synthetase activity in chick embryos. This study is of limited use in quantitating relative potencies, however, because the 2,3,7-tribromodioxin was contaminated with 1% of the 2,3,7,8-tetrabromo congener and the 2,3,7-trichlorodioxin was only 60% (w/w) pure and contained 40% of the 2,7-dichlorodioxin.

Using rat hepatoma H-4-II E cells in an assay for the induction of AHH, Bradlaw and Casterline (1979) noted that 2,3,7,8-tetrachloro-p-dioxin (ED_{50}=1.5 pmol/plate) was ~2 times as potent as the 2,3,7,8-tetrabromo-isomer (EC_{50}=3.7 pmol/plate). Very similar results for these two

TABLE 6-1

Structure-Activity Relationships for Binding Affinity to C57BL/6J Hepatic Cytosol and Induction of Hepatic Aryl Hydrocarbon Hydroxylase (AHH) in Chick Embryo Line, Both Relative to TCDD[a]

Structure	Relative AHH Induction	Relative Binding Affinity
	1.1	ND
	1.0	1.0
	1.0	ND
	0.6 [0.43][b]	0.43
	0.20	ND
	0.02 [0.0006][b]	0.14
	0.01	ND

[a]Source: Kende et al., 1974 (unless otherwise specified)

[b]Poland et al., 1976

ND = Not determined

compounds also were reported by Bradlaw et al. (1980). Two EC_{50} values for the tetrabromodioxin were reported to be 3.64 and 3.85 pmol/plate. The mean ED_{50} value for tetrachlorodioxin was reported as 1.54 pmol/plate with a range from 17 experiments of 0.555-5.024 pmol/plate. Using separate TCDD standards for each assay on the tetrabromo-analog, the brominated compounds had relative potencies of 0.71 and 0.52 with respect to TCDD.

Thunberg et al. (1984) reported similar levels of liver AHH induction in rats given single oral doses (10 μg/kg/day) of 2,3,7,8-TCDD or 2,3,7,8-tetrachlorodibenzofuran and sacrificed 4 weeks after dosing. The chlorinated dioxin caused a greater increase in the activity of microsomal UDP-glucuronyltransferase and a greater decrease in liver retinol concentration and total liver retinol than did the brominated dioxin. Since the molar dose of the brominated dioxin was less than the molar dose of the chlorinated dioxin, the quantitative significance of these results cannot be assessed clearly.

More recently, Denomme et al. (1985) assayed a series of sixteen 7-substituted 2,3-dichlorodibenzo-p-dioxins for binding to the cytosolic receptor protein from male Wistar rats and for the induction of AHH and EROD in rat hepatoma H-4-II E cells. The series of compounds included all four of the 7-halo-dichlorodioxins; results of these assays are summarized in Table 6-2. Both the 7-chloro- and 7-bromo-substituted compounds bound to the receptor protein with about equal affinity, but the bromo-substituted compound was ~6 times more potent than the chloro-substituted compound in the induction of AHH and EROD. For a series of 14 compounds, excluding the phenyl and t-butyl-substituted compounds, receptor binding could be expressed as follows:

$$\log (1/EC_{50}) = 1.24\pi + 6.11 \quad r = 0.95 \qquad (6\text{-}1)$$

TABLE 6-2

Ah Receptor Binding, AHH Induction and EROD Induction by 7-Substituted 2,3-Dichlorodibenzo-p-Dioxins*

Substituent	Substituent Lipophilicity	Binding EC_{50} (mol/ℓ)	AHH EC_{50} (mol/ℓ)	EROD EC_{50} (mol/ℓ)
H	0	7.59×10^{-7}	2.36×10^{-5}	3.65×10^{-5}
F	0.26	1.12×10^{-7}	7.40×10^{-8}	6.70×10^{-8}
Cl	0.83	4.68×10^{-8}	8.94×10^{-8}	6.54×10^{-8}
Br	0.98	4.79×10^{-8}	1.31×10^{-8}	1.00×10^{-8}
I	1.22	5.37×10^{-8}	7.13×10^{-8}	1.25×10^{-7}

*Source: Denomme et al., 1985

where π represents the substituent lipophilicity. As can be noted in lable 6-2, the receptor binding of the four 7-halo-substituted compounds does not appear to be strongly related to lipophilicity. Also within the 7-halo-substituted series, no clear rank order relationship is apparent between receptor binding and AHH or EROD induction. For a series of 11 compounds, excluding the phenyl, t-butyl, carboxymethyl and fused naphthalene-substituted compounds, the relationship between receptor binding and AHH induction could be expressed as follows:

$$\log (AHH) = 1.29 \log (RB) + 2.19\Delta B_5 - 1.31(\Delta B_5)^2 - 2.46 \qquad (6\text{-}2)$$
$$r = 0.963$$

where AHH and RB refer to the $1/EC_{50}$ values for AHH and receptor binding, respectively, and ΔB_5 is the maximum width of the substituents from the axis connecting the 7-substituent to the rest of the molecule. For all 7-substituted dichlorodioxins, a strong correlation was found between AHH and EROD induction potencies:

$$\log (EROD) = 0.99 \log (AHH) - 0.07 \qquad (6\text{-}3)$$
$$r = 0.985$$

As with the relationship between lipophilicity and receptor binding, the relationship between AHH and EROD induction does not appear to be as strongly correlated within the halo-series (see lable 6-2) as within the total group of 16 compounds.

6.3. HALOGENATED DIBENZOFURANS

Denomme et al. (1986) conducted a study on a series of ten 8-substituted 2,3-dichlorodibenzofurans and 13 8-substituted 2,3,4-trichlorodibenzofurans. In each series of dibenzofurans, all four halogens and hydrogen were included as substituents; data on receptor binding and enzyme induction by

these compounds are summarized in Table 6-3. As with the 7-bromo- and 7-chloro-2,3-dichlorodioxins (see Table 6-2), the 8-bromo- and 8-chloro-2,3-dichlorodibenzofurans bound to the receptor protein with about equal affinity as did the 8-bromo- and 8-chloro-2,3,4-trichlorodibenzofurans. In the dichloro-series, the 8-bromo-substituted compound binds with somewhat (54%) greater affinity than the 8-chloro-substituted compound. In the trichloro-, however, the reverse pattern is seen, with the 8-chloro-substituted compound binding with ~56% greater affinity than the 8-bromo-substituted compound. Unlike the 7-substituted 2,3-dichlorodioxins, in which the bromo-substituted compound was ~6 times more potent than the chloro-substituted compound in the induction of AHH and EROD, no remarkable differences are apparent in AHH and EROD induction by 8-chloro- and 8-bromo-substituted 2,3-dichlorodibenzo-furans or in the induction of AHH by the 8-bromo- and 8-chloro-substituted 2,3,4-trichlorodibenzofurans. In the induction of EROD, the 8-chloro-2,3,4-trichlorodibenzofuran is more potent than the corresponding 8-bromo- compound by a factor of ~3.

As in the equation for the binding potencies of the 7-substituted 2,3-dichlorodioxins (Equation 6-1), competitive displacement binding potencies of the full series of 8-substituted 2,3,4-trichlorodibenzofurans and 8-substituted 2,3-dichlorodibenzofurans could be simply related to lipophilicity (π) as described in Equations 6-4 and 6-5, respectively:

$$\log (1/EC_{50}) = 1.09\pi + 5.77 \qquad r = 0.845 \qquad (6\text{-}4)$$

$$\log (1/EC_{50}) = 1.10\pi + 5.19 \qquad r = 0.971 \qquad (6\text{-}5)$$

Equation 6-4 excludes t-butyl- and isopropyl-substituted compounds as outliers and Equation 6-5 excludes the t-butyl-substituted compound as an outlier. There is a reasonably good rank-order relationship between substituent lipophilicity and receptor binding for the 8-halo-substituted

TABLE 6-3

Ah Receptor Binding, AHH Induction and EROD Induction
by 8-Substituted 2,3-Dichlorodibenzofurans and
8-Substituted 2,3,4-Trichlorodibenzofurans*

Substituent	Substituent Lipophilicity	Binding EC_{50} (mol/ℓ)	AHH EC_{50} (mol/ℓ)	EROD EC_{50} (mol/ℓ)
8-Substituted 2,3-Dichlorodibenzofurans:				
H	0	3.97×10^{-6}	2.19×10^{-5}	4.84×10^{-6}
F	0.17	7.08×10^{-6}	3.11×10^{-7}	4.28×10^{-7}
Cl	0.73	6.92×10^{-7}	2.49×10^{-6}	1.56×10^{-6}
Br	0.88	4.47×10^{-7}	2.26×10^{-6}	1.82×10^{-6}
I	1.13	3.72×10^{-7}	4.41×10^{-7}	2.09×10^{-7}
8-Substituted 2,3,4-Trichlorodibenzofurans:				
H	0	2.75×10^{-6}	1.51×10^{-5}	2.48×10^{-5}
F	0.17	5.89×10^{-7}	8.14×10^{-8}	1.37×10^{-7}
Cl	0.73	1.70×10^{-7}	4.14×10^{-8}	3.76×10^{-8}
Br	0.88	2.65×10^{-7}	3.55×10^{-8}	1.17×10^{-7}
I	1.13	2.66×10^{-7}	2.74×10^{-7}	2.95×10^{-7}

*Source: Denomme et al., 1986

2,3-dichlorodibenzofurans (see Table 6-3), although the 8-hydrogen-substituted compound binds with greater affinity than would be expected based on its lipophilicity with respect to the halo-substituents. For the 8-halo-substituted 2,3,4-trichlorodibenzodioxins, the relationship between lipophilicity and binding is less regular, with the 8-chloro-substituted compound binding with greater affinity than would be expected based in the rank order relationship of the lipophilicity substituents of this series. This is similar to the relatively weak relationship noted between lipophilicity and receptor binding affinity in the 7-halo-substituted 2,3-dichlorodibenzo-p-dioxins (see Table 6-2).

The relationship between structure and AHH induction and the relationship between AHH induction and EROD induction for the series of 8-substituted 2,3-dichlorodibenzofurans are described by Equations 6-6 and 6-7, respectively.

$$\log (1/EC_{50})_{AHH} = 0.80\pi + 0.87\Delta B_5 - 0.38(\Delta B_5)^2 + 4.63 \qquad r = 0.951 \qquad (6\text{-}6)$$

$$\log (1/EC_{50})_{EROD} = 0.90 \log (1/EC_{50})_{AHH} + 0.69 \qquad r = 0.942 \qquad (6\text{-}7)$$

In Equation 6-6, the 8-fluoro- compound is excluded as an outlier because its measured AHH induction potency is substantially higher than expected. Both Equations 6-6 and 6-7 are similar to the corresponding relationships noted for 7-substituted 2,3-dichlorodibenzo-p-dioxins given in Equations 6-2 and 6-3, respectively. A different pattern, however, was observed for the 8-substituted 2,3,4-trichlorodibenzofurans:

$$\log (1/EC_{50})_{AHH} = 0.76\pi - 1.11\Delta B_5 + 2.23\sigma + 6.78 \qquad r = 0.948 \qquad (6\text{-}8)$$

$$\log (1/EC_{50})_{EROD} = 0.92 \log (1/EC_{50})_{AHH} + 0.28\pi + 0.27 \qquad r = 0.991 \qquad (6\text{-}9)$$

where σ is the Hammett-substituent parameter, an index of electronegativity. In Equation 6-8, both the 8-H and 8-CH_2Br were excluded as outliers (Denomme et al., 1986). A rationale is not apparent for the requirement of the Hammett-substituent parameter to account for AHH induction and the lipophilicity parameter to account for the relationship of EROD induction to AHH induction in the 8-substituted 2,3,4-trichlorodibenzofuran series, neither of which are required to account for the corresponding relationships in the 8-substituted 2,3-dichlorodibenzofurans nor 7-substituted 2,3-dichlorodibenzo-p-dioxin series (Safe, 1986).

6.4. HALOGENATED BIPHENYLS

In addition to the information on the brominated and chlorinated dioxins and dibenzofurans, several studies are available that demonstrate the effect of bromine vs. chlorine substitution on the biological activity of biphenyls. Analogous to the studies on dioxins and dibenzofurans by Denomme et al. (1985, 1986), Bandiera et al. (1982, 1983) assayed a series of 15 4'-substituted 2,3,4,5-tetrachlorobiphenyls for binding to rat hepatic cytosol receptor and for the induction of AHH and EROD in rat hepatoma H-4-II E cells. Included in this study were all four 4'-halo-2,3,4,5-tetrachlorobiphenyls; the results of which are summarized in Table 6-4. Unlike the results from the assays on 7-substituted 2,3-dibenzo-p-dioxins (see Table 6-2), a clear rank-order correlation is apparent among the halogen lipophilicity parameter, receptor binding and the induction of AHH and EROD for the 4'-halo-2,3,4,5-tetrachlorobiphenyls (see Table 6-4). The bromine 4'-substituted biphenyl binds more tightly to the receptor than the chlorine 4'-substituted biphenyl by a factor of ~1.9. The potencies of the 4'-bromo relative to the 4'-chlorosubstituted compounds in AHH and EROD induction differ by factors of ~140 and 210, respectively. As discussed by Bandiera

TABLE 6-4

Ah Receptor Binding, AHH Induction and EROD Induction
by 4'-Substituted 2,3,4,5-Tetrachlorobiphenyls*

Substituent	Substituent Lipophilicity	Binding EC_{50} (mol/ℓ)	AHH EC_{50} (mol/ℓ)	EROD EC_{50} (mol/ℓ)
H	0	1.4×10^{-4}	inactive	inactive
F	0.14	2.5×10^{-5}	2.7×10^{-5}	1.9×10^{-5}
Cl	0.71	4.7×10^{-6}	3.9×10^{-6}	1.1×10^{-6}
Br	0.86	2.5×10^{-6}	2.8×10^{-6}	5.2×10^{-6}
I	1.12	1.5×10^{-6}	1.1×10^{-6}	2.1×10^{-6}

*Source: Bandiera et al., 1983

et al. (1982), a 4000-fold difference in the potency of enzyme induction, but only a 17-fold difference in binding affinity was observed among all compounds tested. The reasons for these differences in relative sensitivity of the two types of assay systems, enzyme induction and receptor binding, is not clear (Bandiera et al., 1982). Quantitative structure-activity analysis yielded the following equation for the relationship of binding affinity to structural parameters:

$$\log (1/EC_{50}) = 1.53\sigma + 1.47\pi + 1.09HB + 4.08 \qquad (6\text{-}10)$$

where HB is a variable for hydrogen bond formation and σ and π are as described previously. As discussed by Safe (1986), the substantial differences between the complex structural relationships needed to describe the receptor binding of these PCBs and the relatively simple relationships for the dioxins and dibenzofurans (Equations 6-1, 6-4 and 6-5) may be related to the free rotation about the phenyl-phenyl bond of the PCBs.

Ecobichon et al. (1977) assayed the effects of 4,4'-difluoro-, 4,4'-dichloro-, 4,4'-dibromo- and 4,4'-diiodobiphenyls on hepatic p-nitroanisole O-demethylase and aniline hydroxylase activities in male rats treated with 0.2 mmol of agent/kg bw by intraperitoneal injection for 3 consecutive days and sacrificed 96 hours after the third injection. In addition to measuring enzyme activities, compound residues in the liver were also measured. As summarized in Table 6-5, the activities of both enzymes are increased to a substantially greater degree by the dibromobiphenyl relative to the dichlorodiphenyl. While liver residues increase with increasing lipophilicity of the substituent, the diiodobiphenyl is a less potent inducer than either the dichloro- or dibromobiphenyl.

TABLE 6-5

The Effects of 4,4'-Dihalo-Substituted-Biphenyls on Hepatic p-Nitroanisole O-Demethylase and Aniline Hydroxylase Activities and Liver Residues of These Compounds[a,b]

Compound	p-Nitroanisole O-Demethylase (% increase in activity)	Aniline Hydroxylase (% increase in activity)	Residue in Liver (nmol/g fresh tissue)
4,4'-Difluoro-	0	24	NM
4,4'-Dichloro-	33	45	1.71
4,4'-Dibromo-	50	90	2.11
4,4'-Diiodo	9	10	15.8

[a]Source: Ecobichon et al., 1977

[b]Male rats were treated with 0.2 mmol of agent/kg bw by intraperitoneal injection for 3 consecutive days and sacrificed 96 hours after the third injection.

NM = Not measured

The increased potency of bromo-substituted biphenyls, relative to chloro-substituted biphenyls, also has been demonstrated in the study by Andres et al. (1983) using a series of 3,3',4,4'-tetrahalo-substituted bromochlorobiphenyls (lable 6-6). To measure effects on organ weight, groups of four immature (average weight 0.1 kg) male Wistar rats were injected intraperitoneally with each biphenyl at a dose of 150 µg/kg bw, using corn oil (5 mℓ) as a vehicle. Animals were sacrificed and organ weights were determined 15 days after injection. As indicated in Table 6-6, compounds with greater levels of bromination caused greater decreases in thymus weight, with the exception of 3,4-dibromo-3',4'-dichlorobiphenyl, which caused the least reduction in thymus weight of all the compounds tested. Data in Table 6-6 also suggest a clear association between increasing levels of bromination and increases in receptor binding, as well as increases in AHH and EROD activities.

Parkinson et al. (1983) assayed a series of 13 tri- to hexachlorobiphenyls and the corresponding bromobiphenyls in rats for effects on the induction of total hepatic P-450, hepatic epoxide hydrolase, average liver weight and average thymus weight. The results of these assays are summarized in Figures 6-2 to 6-5, respectively. These data are somewhat difficult to compare quantitatively because only single doses of each compound were used, and for some pairs of compounds the molar dose of the chlorinated biphenyl was greater than that of the corresponding brominated biphenyl. To facilitate comparison, Figures 6-2 to 6-5 are constructed so that the points are defined by the response elicited by the chlorinated isomer on the horizontal axis and the response elicited by the corresponding brominated isomer on the vertical axis. The solid line running through the origin defines the line of equal response.

TABLE 6-6

Effects of Various 3,3',4,4'-Substituted Bromochlorobiphenyls on Thymus Weight, Receptor Binding and the Induction of AHH and EROD[a]

Biphenyl	Thymus Weight[b]	Receptor Binding[c]	AHH[c]	EROD[d]
3,3',4,4-Tetrabromo-	31	100	100	100
3-Chloro-3,4,4'-tribromo-	48	78	68	110
3,4-Dibromo-3',4'-dichloro-	81	46	59	56
4,4'-Dibromo-3,3'-dichloro-	55	20	69	43
4-Bromo-3,3',4'-trichloro-	70	24	23	14
3,3'4,4'-Tetrachloro-	78	13	35	14

[a]Source: Andres et al., 1983

[b]Relative to corn oil controls (100%).

[c]Rat hepatoma H-4-II-E cells in culture. Relative (%) to tetrabromobiphenyl.

[d]Immature male Wistar rat hepatic cytosol. Relative (%) to tetrabromobiphenyl.

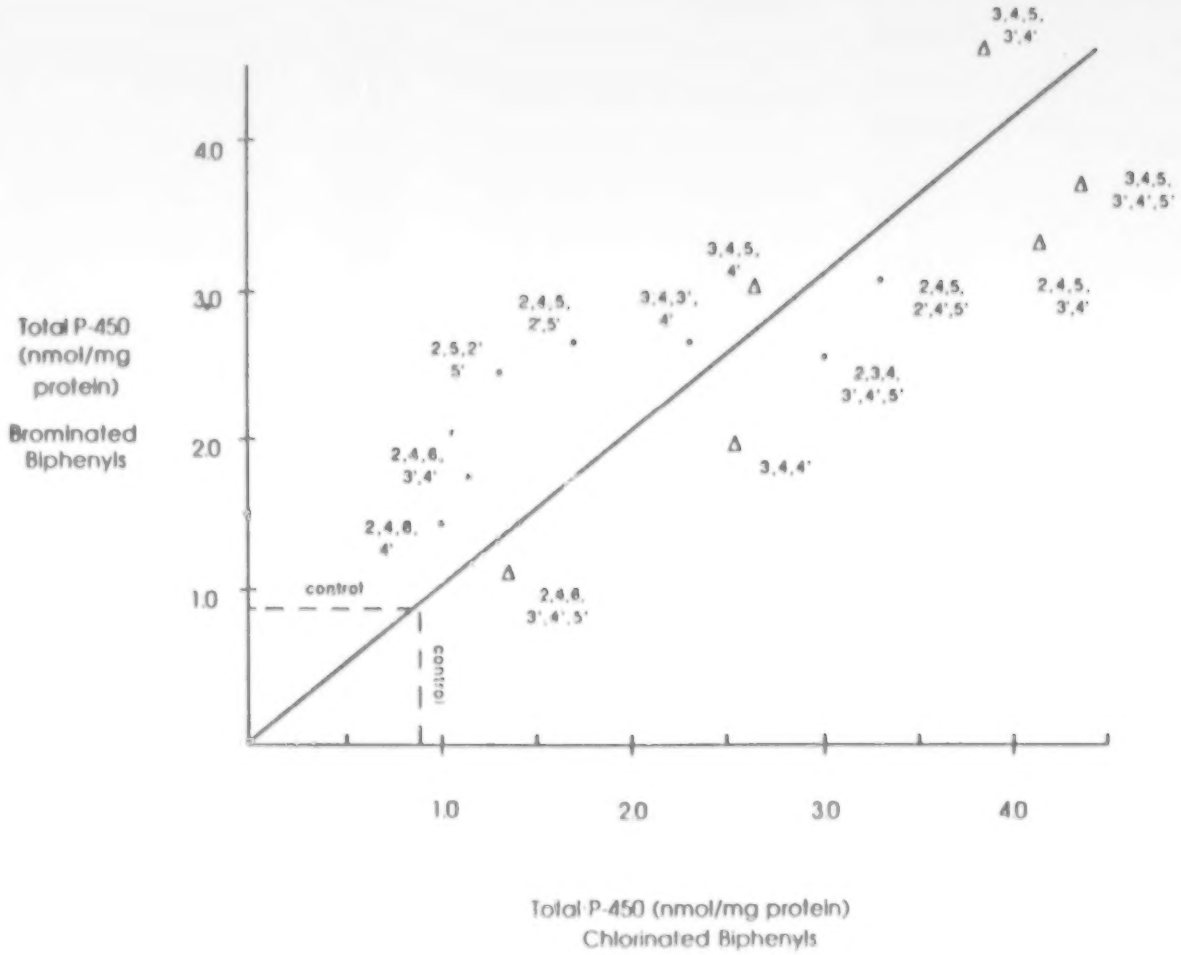


FIGURE 6-2

Comparison of Total P-450 Induction in Rat Liver Microsomes by Chlorinated and Brominated Biphenyls. A Closed Square (■) Indicates Equimolar Doses and an Open Square (□) Indicates Dose of Chlorinated Biphenyl Greater than Corresponding Brominated Biphenyl. Solid Line is Line of Equal Response.

Source: Parkinson et al., 1983

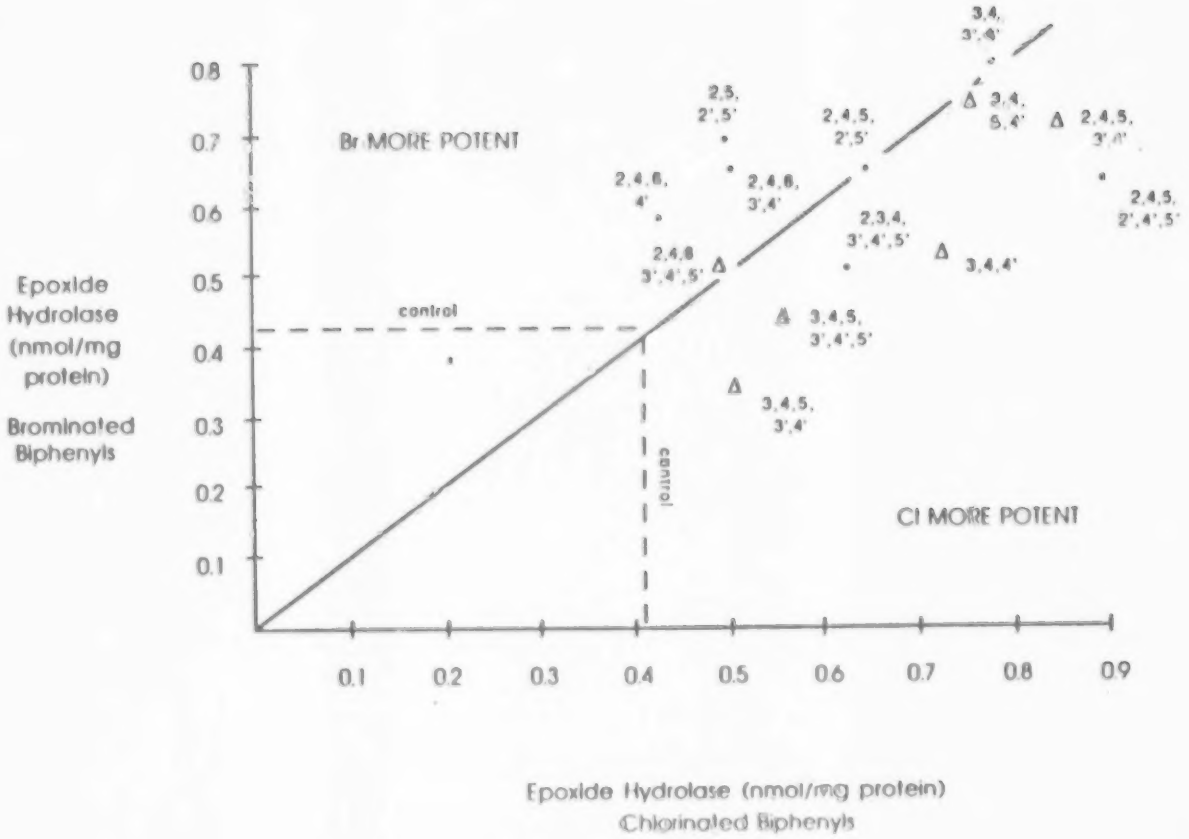


FIGURE 6-3

Comparison of Epoxide Hydrolase Induction in Rat Liver Microsomes by Chlorinated and Brominated Biphenyls. A Closed Square (■) Indicates Equimolar Doses and an Open Square (□) Indicates Dose of Brominated Biphenyl. Solid Line is Line of Equal Response.

Source: Parkinson et al., 1983

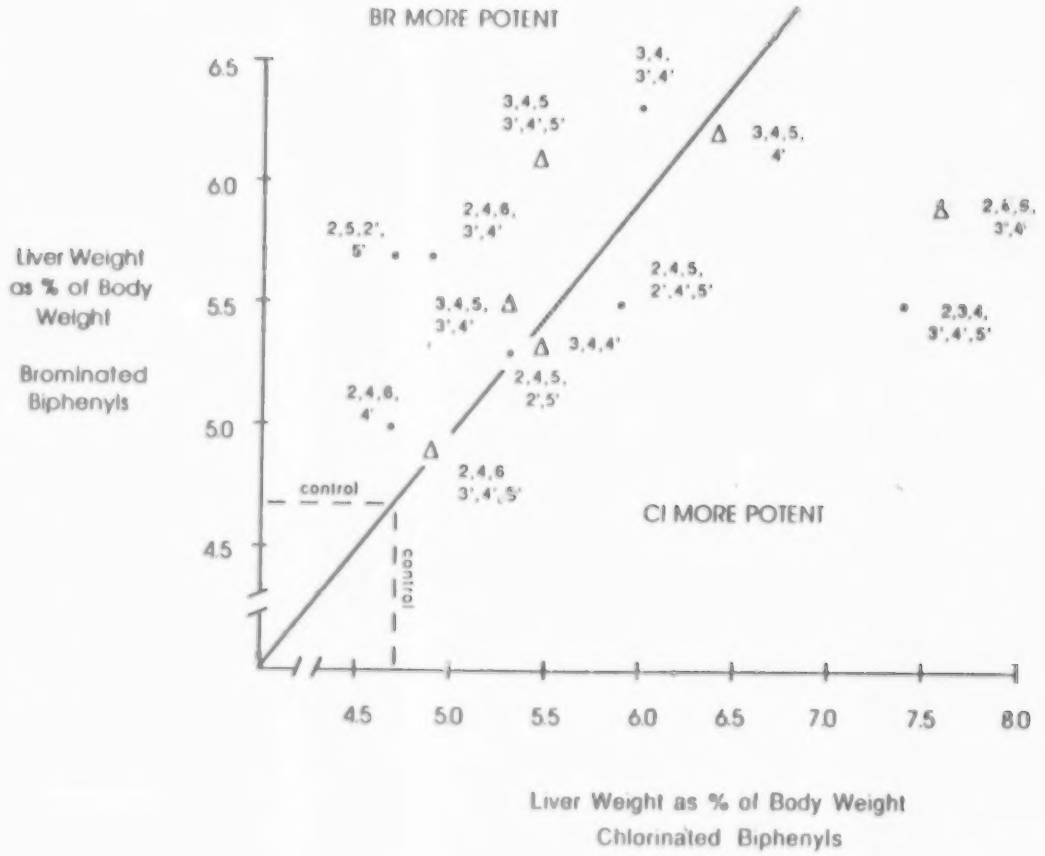


FIGURE 6-4

Comparison of Relative Liver Weights in Rats Exposed to Chlorinated and Brominated Biphenyls. A Closed Square (■) Indicates Equimolar Doses and an Open Square (□) Indicates Dose of Chlorinated Biphenyl Greater than Corresponding Brominated Biphenyl. Solid Line is Line of Equal Response.

Source: Parkinson et al., 1983

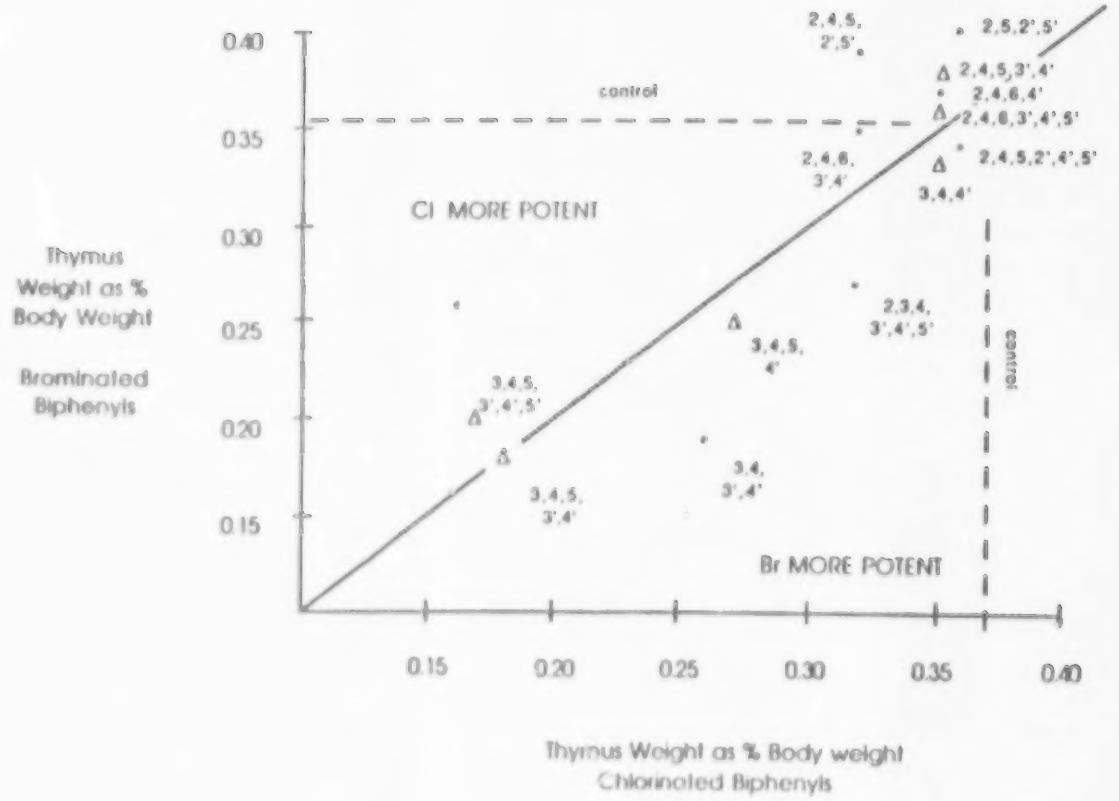


FIGURE 6-5

Comparison of Relative Thymus Weights in Rats Exposed to Chlorinated and Brominated Biphenyls. A Closed Square (■) Indicates Equimolar Doses and an Open Square (□) Indicates Dose of Chlorinated Biphenyl Greater than Corresponding Brominated Biphenyl. Solid Line is Line of Equal Response.

Source: Parkinson et al., 1983

These figures do not indicate a clear pronounced trend in the effect of halogenation on biological activity. In Figure 6-2, for total P-450 induction, the points are about equally and evenly distributed above and below the line of equal response. Since four of the six points which indicate that the chlorinated compounds are more active than the corresponding brominated compounds involved greater molar doses of the chlorinated isomer relative to the corresponding brominated isomer, the general trend suggests a somewhat greater activity for the brominated compounds. A similar pattern is apparent in Figure 6-3 for epoxide hydrolase activity. The greatest deviation from the lines of equal response is seen in Figure 6-4 with 2,3,4,3',4',5'-hexachlorobiphenyl causing a substantially greater increase in liver weight than the corresponding brominated biphenyl. For compounds associated with a decrease in thymus weight (see Figure 6-5), the brominated isomers appear to be somewhat more potent than the corresponding chlorinated isomers. Consistent with the results of Andres et al. (1983), the 3,3',4,4'-tetrabromobiphenyl causes a greater decrease in thymus weight than the corresponding tetrachlorobiphenyl. Both chlorinated and brominated biphenyls (data not summarized in this report) produced similar patterns in the induction of P-450 isozymes (Parkinson et al., 1983).

6.5. OTHER HALOGENATED AROMATICS

As reviewed by Poland and Knutson (1982), other halogenated aromatics have not been as extensively and systematically studied as halogenated dioxins, dibenzofurans and biphenyls. The 2,3,7,8-tetrabromonaphthalene and 2,3,7,8-tetrabromobiphenylene isomers are both somewhat more potent AHH inducers than the corresponding chlorinated isomers (Poland and Knutson, 1982; Poland and Glover, 1977). McKinney et al. (1985a) has demonstrated that 2,4,6-tri-iodophenol binds as avidly to the Ah receptor as 2,3,7,8-TCDD.

6.6. SUMMARY

Quantitative structure-activity relationships have been extensively characterized for chlorinated dioxins, dibenzofurans and biphenyls (Bandiera et al., 1983, 1984; Leece et al., 1985; McKinney et al., 1984, 1985a,b; Poland et al., 1983; Safe, 1986; Safe et al., 1985a,b). Less information is available on the relative potencies of brominated aromatics than the chlorinated aromatics. In early studies on receptor binding and enzyme induction (Kende et al., 1974; Poland et al., 1976), the general relationship of biological activity with respect to differing halogen substituents appeared to follow the order (Br>Cl>F) for a series of halogenated dioxins. Some exceptions to this pattern have been noted (Bradlaw and Casterline, 1979; Bradlaw et al., 1980. Quantitative structure-activity relationships for a series of 7-substituted 2,3-dichlorodibenzo-p-dioxins indicate that receptor binding is highly correlated with lipophilicity and that AHH and EROD induction are correlated with lipophilicity as well as a steric parameter. Both the 7-chloro- and 7-bromo-substituted dioxins bound with about equal affinity to the Ah receptor, but the bromo-substituted compound was a more potent inducer of AHH and EROD by a factor of ~6 (Denomme et al., 1985).

Similar relationships have been noted for two series of dibenzofurans: 8-substituted 2,3-dichlorodibenzofurans and 8-substituted 2,3,4-trichlorodibenzofurans (Denomme et al., 1986). For both series, receptor binding was correlated with lipophilicity. For the former series, both AHH and EROD are correlated with lipophilicity and a steric parameter. For the latter series, AHH induction was related to lipophilicity, a steric parameter, as well as a parameter for electronegativity. The most substantial difference between the 8-chloro- and 8-bromo-substituted compound in both series is in

EROD induction, for which the 8-chloro-substituted 2,3,4-trichlorodibenzofuran was more potent than the corresponding 8-bromosubstituted isomer by a factor of 3.

Structure-activity relationships for the receptor binding of halogenated biphenyls are substantially more complex than those for the chlorinated dioxin and dibenzofuran series summarized above. For a series of 4'-substituted 2,3,4,5-tetrachlorobiphenyls, parameters for lipophilicity, electronegativity and hydrogen bonding were required to account for the effects of structure on receptor binding (Bandiera et al., 1982). Most studies on biphenyls that allow for a direct quantitative comparison of comparative potency of chlorinated and brominated compounds clearly indicated that brominated compounds are more potent (Bandiera et al., 1982; Ecobichon et al., 1977, Andres et al., 1983). In one study (Parkinson et al., 1983) quantitative comparisons were more difficult and the results were equivocal.

Structure-activity relationships for other brominated and chlorinated aromatics have not been well-defined. The limited available data suggest that 2,3,7,8-tetrabromonaphthalene and 2,3,7,8-tetrabromobiphenylene are more potent AHH inducers than the corresponding chlorinated isomers (Poland and Knutson, 1982; Poland and Glover, 1977).

7. RISK ASSESSMENT

The brominated dioxins and dibenzofurans have not been tested for carcinogenicity, mutagenicity, teratogenicity and chronic or subchronic toxicity. Therefore, risk assessments following generally accepted guidelines such as U.S. EPA (1980d) cannot be conducted for these compounds. Nonetheless, the limited available information suggests that these brominated aromatic compounds have toxicological properties and potencies comparable with the corresponding chlorinated compounds. This is consistent with the conclusion reached by U.S. EPA (1985c) in the Agency's proposed rule for requiring that certain commercial products be analyzed for selected brominated dioxins and dibenzofurans.

Very few in vivo studies on the toxicities of brominated dioxins or dibenzofurans that allow for direct comparisons to the chlorinated isomers have been conducted. Yang et al. (1983) noted that single oral doses (25 µg/kg) of both 2,3,7,8-TCDD and 2,3,7-TBDD had comparable effects on ouabain metabolism and liver weights in rats. Because the doses were not equimolar and because the compounds differed in the degree of halogenation, this study is of limited use in quantifying the effect of bromine vs. chlorine substitution. In acute toxicity studies on guinea pigs, Moore et al. (1979) demonstrated that 2,3,7,8-tetrachlorodibenzofuran and the corresponding brominated compound elicited the same types of effects at approximately equimolar doses. As detailed in Chapter 5, these results are consistent with the qualitative and quantitative similarities between chlorinated and brominated biphenyls. Information on carcinogenicity and reproductive effects (Chapter 5) is limited to the chlorinated and brominated biphenyls and chlorinated dibenzo-p-dioxins and suggests that both sets of compounds induce similar biological effects.

The most useful information for quantifying the relative biological activities of brominated and chlorinated dioxins and dibenzofurans is provided by studies of structure-activity relationships in which biological activities are most often assayed as Ah receptor binding, the induction of AHH and the induction of EROD. The results of these studies are reasonably consistent in indicating that brominated isomers are about equal or greater in biological potency to corresponding chlorinated isomers for series of dioxins (Kende et al., 1974; Poland et al., 1976: Denomme et al., 1985), dibenzofurans (Denomme et al., 1986) and biphenyls (Bandiera et al., 1982; Icobichon et al., 1977; Andres et al., 1983). Few exceptions to this pattern have been reported (Bradlaw and Casterline, 1979; Bradlaw et al., 1980), and differences in biological potency are generally within a factor of 3 in instances in which a chlorinated aromatic is more potent than the corresponding brominated aromatic.

While the above data are not directly useful in performing a standard risk assessment, the weight of the limited evidence suggests that the brominated dioxins and dibenzofurans may be as hazardous as the corresponding chlorinated dioxins and dibenzofurans. This presents a difficult problem for the regulatory community because some of the chlorinated dioxins (U.S. EPA, 1985b) are known to be highly toxic and carcinogenic to experimental mammals.

A similar and closely related problem has been addressed by Bellin and Barnes (1985), who have proposed a method for the hazard assessment of chlorinated dioxins and dibenzofurans other than 2,3,7,8-TCDD. For most of these chlorinated dioxins and dibenzofurans, data are not adequate for the assessment of risk using normally accepted procedures. The types of data generally available in these compounds are biological potencies expressed as

acute lethality, receptor binding and enzyme induction. These types of data are also available on many of the brominated dioxins and dibenzofurans. Based on a review of these and other related types of data on the chlorinated dioxins and dibenzofurans, Kellin and Barnes (1985) proposed a series of relative toxicity indices, which are summarized in Table 7-1. A substantial critique of this scheme would require a much more detailed assessment of the biological effects and structure-activity relationships of the chlorinated dioxins and dibenzofurans than has been attempted in this review. Nonetheless, if this system or a modification of this system is accepted by the Agency, the information summarized in this review suggests that the scheme could be directly applied to the corresponding brominated dioxins and dibenzofurans. Using the available toxicological data on a variety of endpoints: carcinogenicity, reproductive effects, acute toxicity, receptor binding, enzyme induction and in vitro cell transformation, and reasoning on the basis of structure-activity relations, the significance of exposure to each congener is estimated and expressed as an "equivalent" amount of 2,3,7,8-TCDD. The relative potency of each congener is then estimated and Toxicity Equivalence Factors are assigned. The relative toxicity factors that have been developed do not (for most isomers) result from long-term animal studies. Generally, they are based on estimates of relative toxicity from in vitro tests whose relationship to the chronic effects of concern is, however, largely presumptive. As more data becomes available, however, the TEFs would be reviewed and revised.

TABLE 7-1

Relative Toxicity Indices for Chlorinated Dioxins and Dibenzofurans[a]

Dioxin		Dibenzofuran	
Isomer	Relative Toxicity[b]	Isomer	Relative Toxicity[b]
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.2	1,2,3,7,8-PeCDF	0.1
		2,3,4,7,8-PeCDF	0.1
1,2,3,6,7,8-HxCDD	0.04	1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.04	1,2,3,7,8,9-HxCDF	0.1
1,2,3,4,7,8-HxCDD	0.04	1,2,3,4,7,8-HxCDF	0.1
		2,3,4,6,7,8-HxCDF	0.1

[a]Source: Bellin and Barnes, 1985

[b]In each homologous group, the relative toxicity factor for the isomers not listed above is 1/100 of the value listed above.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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